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REGIONAL CHARACTERISTICS OF BIOTECHNOLOGY IN THE UNITED STATES:
PERSPECTIVES OF THREE INDUSTRY INSIDERS

Interviews with

Hugh A. D'Andrade
David P. Holveck
Edward E. Penhoet

Interviews Conducted by
Sally Smith Hughes
in 1998 and 1999

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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Cataloguing information:

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Biotechnology executive

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Hugh A. D'Andrade (b. 1938) Executive with Schering-Plough Corp., 1981-present; Schering-Plough alliances with Biogen and DNAX Research Institute; commercializing recombinant DNA technology at Biogen and DNAX; biotechnology in New Jersey; comments on BIO [Biotechnology Industry Organization]. David P. Holveck (b. 1945), CEO Centocor, 1983-present, and work on monoclonal antibody diagnostics and therapeutics, forward integration; partnering with Eli Lilly, corporate culture; biotechnology in Pennsylvania. Edward E. Penhoet (b. 1940), education, Stanford, Illinois and Washington; biochemistry professor, UC Berkeley, 1970-present; president and CEO, Chiron Corp., 1981-1998; discusses Chiron founders, financing, commercialization of recombinant DNA, staff recruitment, corporate growth, bioentrepreneurs.

Interviewed 1998-1999 by Sally Smith Hughes, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

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whose contributions made possible this oral history
of the Regional Characteristics of Biotechnology.

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INTERVIEW HISTORY--Regional Characteristics of Biotechnology

These oral histories with Hugh A. D'Andrade, David P. Holveck, and Edward E. Penhoet are focused on the regional characteristics of the biotechnology industry and also describe the contributions of these individuals to its development. The project, sponsored by the Regional Oral History Office [ROHO] of The Bancroft Library, University of California, Berkeley, and the Chemical Heritage Foundation [CHF] of Philadelphia, is the first step in what we hope will be ongoing documentation of commercial biotechnology in various geographic and business contexts.

The project was sparked by the realization that the biotechnology industry in the United States is two decades old and yet no thorough historical study of the early stages of the industry and its pioneering figures has been made. Without such an effort, there is a danger that the distinctive characteristics of the industry in its earliest manifestation will be lost to memory as the twenty-first century advances. We started with the assumption that regional concentrations of biotechnology along the East and West coasts would exhibit different attributes. The three oral histories represented in this volume suggest that our impression is borne out, at least in the San Francisco and Pennsylvania/New Jersey areas. Yet there are also commonalities, such as the necessity for corporate access to basic science expertise and the important role of entrepreneurial individuals. Documentation of the extent, diversity, and complexity of these distinctions and similarities requires further interviews in other geographic settings and corporate and academic environments.

Hugh D'Andrade, currently vice chairman and chief administrative officer of the pharmaceutical company Schering-Plough of New Jersey, was selected as a voice from "Big Pharma" on its early relationship with biotechnology. Schering-Plough had collaborated in the 1970s with Cetus Corporation of California on its flagship (but commercially unspectacular) process for antibiotic screening. When D'Andrade joined Schering-Plough in 1981, he began to administer the company's collaboration with Biogen, a small company formed in 1980 to capitalize on the commercial potential of recombinant DNA. Schering-Plough's third and enduring relationship with biotechnology is with DNAX Research Institute, founded in California in 1980 and acquired by Schering-Plough in 1982. All three were risky endeavors at a time when commercial biotechnology was in its infancy. Although no tangible products were immediately forthcoming, D'Andrade views these associations as building corporate capability in cutting-edge science and providing Schering-Plough with the prestige of ties with leading academic scientists, including DNAX founders and Nobel laureates, Arthur Kornberg and Paul Berg. As a participant in the heady discussions surrounding the race to

clone the gene for interferon and other early targets of genetic engineering, D'Andrade conveys the excitement and competitiveness of the early days of applied genetic engineering.¹

David Holveck, presently CEO of Centocor, a biotechnology company in Malvern, Pennsylvania, provides a contrast to Schering-Plough's genetic-engineering-at-a-distance approach to the technological breakthroughs which molecular genetics offers in drug discovery. In a pattern reflected in the formation of other start-up companies in the early days of commercial biotechnology, Centocor was founded by entrepreneurs hoping to capitalize on monoclonal antibody-hybridoma technology as a novel method of pharmaceutical production. With the company's eggs primarily in this technological basket and its focus primarily on one drug, Centocor in the early 1990s was brought close to disaster. Holveck describes in the interview how he was promoted to chief executive officer for the purpose of salvaging the company when the drug failed in clinical trials. With help from his colleagues, he succeeded in doing exactly that. Like D'Andrade, Holveck speaks of the importance of personal interaction and corporate culture in a company's fortune.

Edward Penhoet, former chief executive officer of Chiron Corporation and current dean of the University of California, Berkeley, School of Public Health, is the subject of the third interview. He was selected for an oral history because of his role in the pioneering years of the biotechnology industry and because his West Coast location provides a vantage point from which to compare and contrast the East Coast view of biotechnology as described by D'Andrade and Holveck. Penhoet tells of his personal odyssey from medical student at Stanford to biochemistry professor at Berkeley to co-founder of Chiron in 1981. He is well positioned at the intersection of university science, technology, and the business of biotechnology to comment on the elements shaping biotechnology in northern California.

But what of the major theme of this volume, the regional characteristics of biotechnology and their implications for the industry's geographic concentrations? Access to basic science and the scientists with expertise to practice it is seen by all three interviewees as a prime necessity for a company applying any form of genetic engineering. Holveck and Penhoet place proximity to research

¹ For the views of DNAX founders on the relationship with Schering-Plough and other details of DNAX history, see: Arthur Kornberg, *Biochemistry at Stanford and Biotechnology at DNAX*, and Paul Berg, *A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry*, oral histories conducted by Sally Smith Hughes, Ph.D., Regional Oral History Office, The Bancroft Library, University of California, respectively 1997 and 2000.

universities as a prime prerequisite. Yet D'Andrade describes how Schering-Plough--successfully in his eyes--reached across a continent to acquire capability in the new molecular technologies. The interviews also suggest explicitly or implicitly the role in biotechnology ventures of personal characteristics, often expressed as entrepreneurial drive, risk tolerance, and vision. Another factor is corporate culture. Penhoet particularly speaks of the need to replicate in industrial settings some of the attributes of academia in order to attract and retain university scientists.

The Oral History Process

Although all three interviews were conducted by Sally Hughes (with the assistance in two cases of CHF historian of science Leo Slater), CHF supported and arranged the interviews with Mr. D'Andrade and Mr. Holveck; The Bancroft Library supported the two interviews with Dr. Penhoet. Mr. D'Andrade was interviewed in his office at the Madison, New Jersey location of Schering-Plough on November 6, 1978. Mr. Holveck was interviewed at Centocor in Malvern, Pennsylvania on February 2, 1999. Two interviews were recorded with Dr. Penhoet in the Office of the Dean in the School of Public Health at Berkeley on September 11 and 30, 1998. CHF transcribed and produced in separate volumes the interviews with D'Andrade and Holveck; the Penhoet interviews were transcribed at ROHO. All three men reviewed and approved the interview transcripts. In 2000, ROHO decided to produce the three sets of interviews in one volume so that views on the regional characteristics could more readily be compared and contrasted. In conformity with ROHO procedure, the transcripts were re-edited and headings, tables of contents, this interview history, and other aids to the reader added. The reformatted versions were approved by D'Andrade and Holveck; Dr. Penhoet, with some assistance from William Staggs at Chiron, edited and approved his transcripts.

The Regional Oral History Office was established in 1954 to augment through tape-recorded memoirs the Library's materials on the history of California and the West. Copies of all interviews are available for research use in The Bancroft Library and in the UCLA Department of Special Collections. The office is under the direction of Ann Lage, Acting Division Head, and the administrative direction of Charles B. Faulhaber, James D. Hart Director of The Bancroft Library, University of California, Berkeley.

Sally Smith Hughes, Ph.D.
Historian of Science and Project Director

January 2001
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REGIONAL CHARACTERISTICS OF BIOTECHNOLOGY IN THE UNITED STATES:
PERSPECTIVES OF THREE INDUSTRY INSIDERS

Hugh D'Andrade

An Interview Conducted by
Sally Smith Hughes
in 1998

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INTERVIEW WITH HUGH A. D'ANDRADE

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Regional Oral History Office
Room 486 The Bancroft Library

University of California
Berkeley, California 94720

BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name Hugh A. D'Andrade

Date of birth November 7, 1938 Birthplace Plainfield, N.J.

Father's full name Herman Edwin D'Andrade

Occupation Executive Birthplace Trinidad

Mother's full name Lucile Peticolas

Occupation -- Birthplace Omaha, Neb.

Your spouse Mary V. Toner

Occupation Teacher Birthplace Perth Amboy, N.J.

Your children Janine

Where did you grow up? Metuchen, N.J.

Present community Summit, N.J.

Education B.A. Rutgers University, 1961

LLB Columbia Law School, 1964

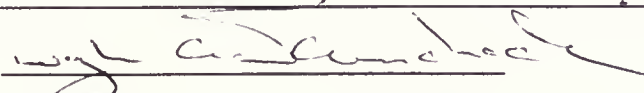
Occupation(s) Executive

Areas of expertise _____

Other interests or activities _____

Organizations in which you are active Drew University,

Columbia Law School, Overlook Hospital

SIGNATURE  DATE: 10/27/00

INTERVIEW WITH HUGH A. D'ANDRADE

I EDUCATION AND EARLY CAREER

[Date of Interview: November 6, 1998] ##¹

Hughes: Please tell in brief your background and education.

D'Andrade: I've lived in New Jersey all my life. I grew up in Metuchen, which is about five miles from New Brunswick. I graduated from high school and went to Rutgers in New Brunswick and commuted from home. I got my degree in economics, and then went to Columbia Law School and continued to commute, from home to New York. I graduated from law school [in 1964]. I clerked for a justice [Frederick W. Hall] in the New Jersey Supreme Court for a year [1964-1965], whose chambers were in New Brunswick. Then I went to work for a law firm in Newark [Toner, Crowley, Woelper & Vanderbilt] and worked there for about three years. I was not very happy in the private practice of law. We had a lot of very large clients and did a lot of the litigation in defense of those clients. I felt I was always dealing with a set of facts that were already fixed, that had created a problem for the client, and that they had brought to the law firm to help them with the trouble that they had gotten into and that it would be more fun and more challenging to be a counselor, to be able to do something about facts before they created a problem.

So I began to look at opportunities for corporate counsel. I saw an ad for Ciba Corporation. I only had a vague idea of what Ciba was. I interviewed for a legal position at Ciba in Summit, New Jersey, which is just two miles from here. I liked what they said they were doing. It sounded like a good job. They offered me the job. There were two attorneys and I became the third. That was 1968. Ciba was a subsidiary of a Swiss chemical and pharmaceutical company with an agricultural chemicals business, a dye business, a small consumer products

¹## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

business and, of course, a drug business, and a plastics and additives business. The three of us attorneys worked in all of those areas, but I became particularly involved in FDA [Food and Drug Administration] matters. I became really very knowledgeable about food and drug law and enjoyed that a lot.

Then there was the merger between Ciba and Geigy. I picked up one piece of management responsibility or another so that by 1981, when I left Ciba-Geigy, I was [senior] vice president of administration in the pharmaceutical division. I also was still chief counsel for that division. Then I went over to Schering-Plough [in 1981] as [senior] vice president of administration and planning and had the same sort of responsibilities, with the general counsel reporting to me, and a lot of other administrative functions.

Hughes: Why did you make the shift?

D'Andrade: I made the shift because at Ciba-Geigy, a Swiss-owned company, most of the critical strategic decisions were made, as they ought to have been, by people who were running the company in Switzerland. It was a little bit the way I felt when I left the law firm; I was being given decisions to implement and wasn't very involved in their formulation, and I had an opportunity to move up to the next level of decision making.

II SENIOR VICE PRESIDENT TO VICE CHAIRMAN AND CHIEF EXECUTIVE OFFICER, SCHERING-PLOUGH CORPORATION, 1981-PRESENT

Arrival, 1981

D'Andrade: A lawyer I worked with at Ciba, Bob [Robert P.] Luciano, had meanwhile moved out of the legal area into the management area at Ciba-Geigy and then had gone over to Lederle and become president of the Lederle pharmaceutical business within American Cyanamid. He then moved over to Schering-Plough, and when he was promoted to president of pharmaceuticals--or maybe it was executive vice president--the job he had as vice president of planning and administration is the one I took. He had known me at Ciba, and we had kept in touch. He invited me come over and I said, "Yes." I've been doing pretty much the same thing here since 1981.

Nature and Quality of In-house Research, circa 1981

Cetus Corporation's Microbial Screening Method

Hughes: What did you find in terms of the research endeavor at Schering-Plough when you arrived?

D'Andrade: The research that Schering-Plough was doing was very traditional. It was organic chemistry, screening of the organic compounds that chemists built, based on whatever leads they were working on. And there was an effort to find new antibiotics through the screening process in an automated screening lab with a lot of soil samples and other sources of antibiotics to be put through that antibiotic screen. I never got a sense of whether that was a rational effort. I don't

think that automated effort turned up a hit. Not to my knowledge.

Hughes: No relationship to the method that Cetus was pushing?

D'Andrade: Well, it was a connection we had with Cetus, that was designed to help our antibiotic screening effort, that was already in place when I joined Schering-Plough. I never got clear in my mind what Cetus was doing for us, or if I had it in my mind, I've lost it. But some of the early biotech work Cetus was doing was thought to be useful for us in our antibiotic effort, and I think it was in the screening effort.

Hughes: Cetus was founded in 1971 on the basis of microbial screening technology.

D'Andrade: Yes. The people at Schering, Bob Luciano I think specifically, came to know one of the venture capitalists, the founder of Cetus, Moshe Alafi, as a result of that collaboration and the negotiation for the antibiotic screening effort. Then Moshe became one of the venture capitalist founders of Biogen. So when Biogen was looking for companies to work with, Moshe came and talked to Luciano. It gets a bit off your point of what I found in the research effort [at Schering-Plough].

A Traditional Chemical Approach to Drug Discovery

D'Andrade: As I said, it was a traditional chemistry effort and it was this antibiotic screening effort. My sense, without having the expertise to know, is that the chemists were pretty good. But we didn't have a lot of horsepower going in that chemistry effort, and I would guess that our screens were no more than what everybody else had. We had no competitive advantage in our ability to screen compounds we were working on. There was probably some rigidity in willingness to look for new chemical avenues to explore. So I wouldn't say our research effort was successful at that time or could have been described as even first-rate; it needed some reinvigoration and some shaking up.

Hughes: Had you been aware of that before you accepted the position here?

D'Andrade: No, and it wouldn't have occurred to me to try to figure that out. At Ciba, I certainly did not have a role, from a strategic point of view, in guiding the research effort. That was really done in Switzerland, although there was a sizable

research organization in Ciba-Geigy's operation in Summit, run by some very good people. Those people in Basel, together with the head of research, Hugo Bein, made the decisions about where research was going, what fields they'd work in, what leads to take up within given fields. So I was very involved with the research guys at the level of defending our efforts with FDA, but not at the higher level of what those efforts ought to be. So the answer is, no. I didn't have any idea of how the research effort at Schering-Plough ranked as compared to others.

Biogen and Commercial Biotechnology

Moshe Alafi

Hughes: Continue with Alafi and his proposal to Luciano.

D'Andrade: Now, that was before I came, but I've heard about it both from Moshe and Bob, and I see the evidence of it in our agreements with Biogen. Bob was very interested in doing some projects with Biogen because he saw that with the antibiotic effort and the organic chemistry effort, we were just doing the same things that all our big competitors were doing, whether it was Merck or Pfizer or Lilly [Eli Lilly and Company]. We didn't have a competitive advantage in either of those areas and thought that biotechnology offered us a chance to work in a field where we were on an equal footing with all the other big pharma companies.

Hughes: This was coming through Alafi?

D'Andrade: No. Well, I can't say that. I wasn't here.

Targeting the Interferons and Erythropoietin

D'Andrade: I've come to know Moshe very well, and he was certainly quite knowledgeable for a venture capitalist as to the science, and he doubtless discussed it with Luciano. But at that time, Luciano had brought about a change in research management. A fellow named Alex Lane took over, and I think Alex was more open. I suppose that Bob and Alex talked about the science, but I don't think that was the hard part of the decision. Bob

said, "Okay, I understand there's a new science developing here," and maybe Cetus pioneered it, maybe Genentech was really the one who took the lead. Biogen's run by all these very bright scientists, all of them have worldwide reputations. For the amount of money--that was not extraordinary by Schering-Plough's standards at the time--Bob was able to get in on the ground floor with Biogen in search for the products that were on, frankly, everybody's radar screen. Saying you wanted interferon didn't take somebody who had been reading *Scientific American* for the last six years. Really, as a lay person, he was up on what was going on. Cetus was looking for beta-interferon; Genentech was looking for it; Biogen was looking for the interferons.

Hughes: Were you aware of the hype about the interferons as potential therapy for cancer and viral diseases?

D'Andrade: Yes. I'll come back in a moment to answer that question because it requires me to ratchet back a little bit.

The other project that Bob selected for Biogen to do was erythropoietin. That was a little less obvious, and that was because the head of research whom Alex Lane replaced, a gentleman by the name of [Douglas] Larrison, a physician, was a hematologist, and Larrison had stayed on in a role as senior vice president for science. Larrison pushed the erythropoietin project.

Hughes: Please come back to the question of hype concerning interferon.

D'Andrade: Yes, there was a lot of hype or buzz about interferon, which I guess was due to the work done by [Kari] Cantell, using the small amounts that he was able to purify from human blood. It promised to be a miracle drug. So it's not surprising that so many of the early biotech companies went looking for the gene that coded for interferon.

Monitoring Developments in Biotechnology

D'Andrade: Now, back to what I would have been aware of at Ciba-Geigy. I was responsible for the business development effort at Ciba-Geigy--going out and licensing new products, making research arrangements with small companies. So I tried to keep myself up to date on what was going on in science, particularly in things I viewed as tools and technologies because there I could deal directly with the science. Summit would not have to

convince somebody in Basel that we ought to strike out into a whole new area. So I kept an eye on what was going on in biotechnology.

Hughes: How did you do that?

D'Andrade: I don't remember. I read the stuff that people read, the trade [journals].

Hughes: Advances in biotechnology were frequently reported in *Science*, for example. Did you ever read *Science*?

D'Andrade: I don't remember whether I read *Science* regularly at the time. I've been reading it so long, I don't remember when I started. I read *Nature* regularly.

Hughes: It was in there, too, of course.

D'Andrade: I don't read *Nature* anymore. I couldn't get through them both. I had to make a choice. But biotechnology was just in the atmosphere, and there were companies coming and calling on us. My recollection is that probably in 1979-1980, I was most interested in monoclonal antibodies. That's what I thought was really going to be a successful therapy.

Hughes: Why did you think that?

D'Andrade: I don't remember. Probably because the technology seemed more obvious to me. You get the hybridomas; you can make the antibodies; they can be targeted pretty exquisitely, and it just seemed to me that that's the thing that was going to go ahead. It was the go-ahead part of biotechnology. The business of building DNA libraries and looking for genes that coded for specific proteins that you clone and put in hosts--either that didn't seem to me to be practical or a near-term project, or I didn't understand it, or a mixture of both.

Hughes: Well, you were close to right. As I remember, the first product of modern biotechnology was indeed diagnostic tests based on monoclonals.

D'Andrade: Yes.

Member of the Biogen Board of Directors

D'Andrade: When I came to Schering-Plough, the Biogen agreement was already in place and the first thing Bob did was say, "You go on the Biogen board." Because we'd bought stock, we had the right to have someone on their board. He said, "You go on the Biogen board in my place, and you take over the interferon project."

Hughes: Why did he say that?

D'Andrade: I think because he didn't want to do it anymore himself. He had a lot of other demands on his time. Running the interferon project internally, though Bob stayed very close to it, was not only demanding of his time, but there are levels of management which you reach and it becomes inappropriate to do certain kinds of things even though you may want to. The president can't run the interferon task force because if he sat down in a room with everybody and said, "Well, I think we ought to do something. What do you all think?," they'd all say, "You're right." Whereas, if I sit down, they'd say, "No! You're all wrong. We've got to do this. We can't do that; it won't work."

So anyhow, I immediately began going to Biogen's scientific board meetings, which always preceded the general board meeting. The meetings were in Geneva because that's where the company had its corporate offices and its laboratories. There would be a two-day scientific board meeting before each board meeting. Two full days. Bob said, "Look, go sit in on the scientific board meetings. You'll learn something." They were real events. Phil [Philip] Sharp, Wally [Walter] Gilbert, Bernard Mach, Walter Fiers, Charles Weissmann, sometimes a guy called Tanangucci would come, Jeremy Knowles--just a whole bunch of extraordinary people working in this field [recombinant DNA]. And for two days they'd argue with each other and they'd give reports.

Biogen Scientists

D'Andrade: The way Biogen was operating at that time, although they had their own laboratories in Geneva and some of their own scientists, 80 percent or more of the research effort was being done in the individual labs. So Weissmann had the interferon project, and he was doing that in his lab in Zurich, and

Bernard Mach and Walter Fiers had been given the erythropoietin project.

Hughes: Where were they?

D'Andrade: Bernard Mach was in Geneva, and Fiers was in Amsterdam, I think. All university scientists, all working in their own laboratories.

Hughes: Did that cause controversy as it did in this country?

D'Andrade: No. Biogen had agreements with each of those universities put in place to permit those people to be on the Biogen scientific board and to do work for Biogen and to give Biogen rights. I don't think it created the sort of controversy or interest that the involvement in industry of, say, some of Stanford's scientists did. I don't think it was because the universities in Geneva or Zurich or Amsterdam--I think Knowles was working at the University of Scotland--were more sophisticated than Stanford or Harvard. I think it may have even been because they were less.

Hughes: Yes.

D'Andrade: The research was clearly basic--at least it had a lot of the characteristics of basic research. It didn't seem that it was something their scientists wouldn't be doing anyway. Everybody was chasing after the idea of being able to actually produce human protein outside the body through the use of a human gene. Now we all take it for granted, but it was really an extraordinary idea. Sure, there'd been evidence that you could create a recombinant organism. But the idea you'd actually be able to say, "I want erythropoietin," and then get it.

People would argue. I can't even remember what we argued about. "Did it have to be glycosolated?" "It doesn't have to be glycosolated." "What are going to be the effects of growing it in microorganisms like *E. coli*? How are we going to control it?" The first fermentation equipment we put in to do just a little bit with interferon in Bloomfield [New Jersey] was, I think, at the P3 [physical containment] level.

Hughes: Well, the NIH [National Institutes of Health] recombinant DNA guidelines were in place.

D'Andrade: Yes. The idea that all of this was going to create disasters was all around.

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D'Andrade: I think those universities saw this as the thing their guys were going to be doing anyway. Biogen had a European orientation and European lawyers, and they said, "Okay, we'll do these agreements." So the answer to your question is: no, to my knowledge it didn't create any controversy.

Hughes: How did Schering-Plough's relationship with Biogen evolve?

D'Andrade: Well, Biogen was an organization that was in constant conflict and turmoil for two very obvious reasons, I think even obvious at the time. Because the work was all being parceled out to these laboratories, there was no centralized decision-making structure. There were no regular interactions, other than the scientific board, that would allow the scientists to coordinate their actions, and there was no executive authority. There was a president of Biogen sitting in an office in Geneva, but you have Fiers in Amsterdam, Knowles in Scotland, Mach in Geneva, Weissmann in Zurich, Gilbert in Harvard, and Sharp at MIT. Those are the only people I can remember right now. There were a whole lot more. So the structure guaranteed confusion and conflict. And then the personalities of the people would have guaranteed it no matter what structure you had. [laughter]

Hughes: Give us a little flavor of what some of those board meetings were like.

D'Andrade: Well, the scientific board meetings were quite interesting because somebody would get up and make a presentation, and then Wally Gilbert, who was chairman of the scientific board--I don't know whether Wally tried to humiliate; I couldn't read his mind. And being a non-scientist, I couldn't appreciate exactly what was going on. But it looked like the guy presenting wasn't having a lot of fun!

Charles Weissmann is a gentler soul, but could be pretty tough. They'd have the lab scientists present. Particularly guys from Geneva would present what they were doing, and the members of the scientific board would go at them, and then go at each other. So it was very, very rigorous.

Hughes: And personal?

D'Andrade: If it was, I missed it.

Hughes: So the discussion seemed to be strictly on a scientific level?

D'Andrade: Yes, it was on a scientific level. That doesn't mean people didn't take it personally, but I didn't catch any personal attacks. It always seemed to be that the attack was on the

science. Now it would be quite possible for me not to see the difference between an attack on the science and a personal attack. What I felt was that while there was a whole lot of intellectual rigor occurring during those scientific board meetings, it didn't fix whatever the problem was when it was all over. It was as if just pulling the skin off and looking inside would be surgery enough. But it wasn't, and it seemed to me it should have been somehow followed up. But again, there was no real executive authority after the scientific board meeting to say, "Well, then we ought to do this; we ought to do that; we ought to do the other thing." And then call Mach or Weissmann or Fiers or Gilbert and say, "Well, as a result of that meeting, I've concluded that we're really going down the wrong direction here, or we've got to put more people on this, or we've got to take people off that."

Hughes: Was there also the problem that the research for Biogen was not the only thing that these academics were doing? Or was Biogen really the center of their scientific life at that moment?

D'Andrade: I don't know. I don't think I'm wrong in saying Weissmann was working eighteen to twenty hours a day on interferon. I don't know that he wasn't doing something [else] with the other two hours or four hours. I know some of the others weren't working as hard. I think Fiers was. I think Gilbert was probably juggling a number of things.

Problems with Biogen Organizational Structure

D'Andrade: I've said there was a lack of executive authority and decision-making to take advantage of what was coming out of the scientific board meetings. Another way of saying that is that there was a lack of coordination, and I think there's at least two ways to look at how things can be coordinated. You can coordinate between laboratories, and there certainly, in my judgment, was a lack of coordination between Mach's lab and Fiers' lab. Both of them were working on erythropoietin. But you can also coordinate within a lab. You can say, "Okay, Charles, what are you doing? How far are you down this road? Maybe you ought now to be going over there." So there probably were some projects that were badly organized, perhaps staffed or resourced in other ways, within any given scientific board member's laboratory. I don't know.

- Hughes: Couldn't coordination have been your function? You were the Schering-Plough representative on the Biogen board. Could you have imposed some organization?
- D'Andrade: No, I could not have supplied the executive authority. I didn't have it within the Biogen organization. I was a visitor at the scientific board meetings.
- Hughes: So you were there at their grace, so to speak.
- D'Andrade: I was a member of the board. Biogen's unique organizing concept when it set itself up was that it was run by its scientists, not by the venture capitalists, the banks. If you look at the early charter for Biogen, it really makes that clear. The scientific board had the right to elect to the Biogen board quite a few of the scientists. When Biogen was formed originally by Gilbert and Sharp--
- Hughes: And Weissmann, I think.
- D'Andrade: I think Gilbert went to Weissmann, or maybe Weissmann and Gilbert came together spontaneously. When they went to the scientists, they said, "Look, you don't have to quit your lab and go to work for [Biogen] like you're working for Genentech, and you don't have to have somebody from the company telling you what to do. The scientists are going to run this company. The scientists are going to pick the projects." It was clear. The scientific board picked the projects, not somebody that the venture capitalists put in as president. They picked the projects; they abandoned the projects. They chose the scientists who were assigned the projects, and they even supervised the research in the corporate Geneva lab. One of the purposes of the scientific board meetings was to have those scientists present their work over the previous three months, or whatever the span of time was, to the scientific management of the company.

Now, do I think that that organizational structure contributed to why Biogen didn't succeed in some of the things it was looking for as compared to others? I think in retrospect, we might say, "Yes, getting erythropoietin was more of a brute force project than getting interferon." Look at what [Hoffmann-La] Roche, Genentech, and Weissmann did. So Amgen had an advantage with erythropoietin because it's hierarchically structured and they had the scientists in the lab.

More on Erythropoietin

Hughes: Why do you call erythropoietin a brute force effort?

D'Andrade: It's just my sense of the manner in which Amgen was successful in cloning erythropoietin using what they call, I think, a "zoo blotting" technique, where they used other mammalian [DNA] libraries and got erythropoietin from some other primate and then used that. My impression at the time, trying to understand why Amgen was successful and Biogen wasn't, was that Amgen used more brute force than Biogen. I could be entirely wrong. But in any event, certainly in screening some libraries or getting some proteins, brute force is useful. To the extent that brute force was useful, Biogen didn't have the techniques or the desire to apply it. Charles had interferon and he was going to keep interferon. He used a couple of people in his lab, but that's all.

Slater: Did you bring home any lessons when you got off the plane from Geneva?

D'Andrade: I didn't say it to myself in so many terms, but I can now certainly claim that when the opportunity to buy DNAX came along, I said, "The assets here are the scientists." The particular projects were a little interesting, but they weren't so much interesting to us. I mean, it was necessary that those projects were in the field of immunology, but the specifics of them, which was also some antibody work, weren't. By that time I had gotten over antibodies and was interested in human proteins, cellular proteins.

What I very much wanted and talked to Luciano about was having our own group of molecular biologists who could work in the field of immunology. I said, "Let's stop relying on agreements with Biogen or Cetus." We were canvassing the field at that time. We were talking to everybody who had projects in recombinant DNA. I said, "Let's put our own group of scientists together." I think that was because I felt that management had an important role to play in the success of those efforts. So I guess I did take a lesson away from watching the chaos of Biogen.

Resistance to Biogen within Schering-Plough

- Hughes: Did you have to come back from these meetings and sell the Biogen relationship? Or was Luciano behind you and that was all you needed?
- D'Andrade: I think that most of the research group in Schering-Plough didn't particularly like the Biogen relationship. They understood that Luciano had staked his own reputation on it, and they clearly understood that I was his hammer. I banged on them pretty hard and was young enough and naive enough that I didn't look for evidence that there was resistance.
- Hughes: What was the basis of that resistance?
- D'Andrade: I think the fundamental reason for the resistance was that the research people, as distinguished from the development people, had their own efforts and projects that they were working on. When it came to dealing with issues of: "What more can we do to help Biogen succeed with erythropoietin? What more can we help Charles with to take the first clone he got and turn it into something that was capable of being reproduced?," there were a lot of difficulties. There was arguing about whether they were due to assay differences, or whether there was some other reason for it. They had their own stuff to do. This was a bolted-on project, if you will.

I've come to recognize that if you bring a project in from the outside, whether it's a Biogen project or a Centocor project or anybody's, then the research people here say to themselves, "If this is a big success, everybody's going to say, 'Boy, it's a really good thing we did that deal with Biogen. Isn't that Charles Weissmann terrific?' If it's a failure, they're going to say to me, 'Why did you let that project fail?'" So even for the head of research, the head of discovery research, the director of molecular biology [at Schering-Plough], however you do it, all that can happen once you say, "We're working with Biogen to get interferon," is: they [the Schering-Plough scientists] fail or Biogen succeeds. This is not an equation that they love to deal with. You say, "Well, you've got to create a sense of ownership and break down the impression of winners and losers." It's pretty hard. There are ways to do it.

We tried to do it with DNAX, not entirely successfully. One of the ways to do it is to bring in new people who are not vested in projects that exist and let them be largely responsible for the projects you do select with the outside

party. If the head of discovery research says, "I want to work with Cephalon in looking for something to deal with Alzheimer's," you get a different result than if I, knowing we want something in the field of Alzheimer's, survey the universe and say, "I think Cephalon and Regeneron are one and two. We can do a better deal with Cephalon. So here's the deal. Now, start working with Cephalon."

There's a world of difference. If you bring in somebody new and say, "Okay, now, what are we going to do in the field of Alzheimer's? Let's look outside." And then you give that person the responsibility for coming back and saying, "Cephalon and Regeneron are one and two. I like Cephalon better." You say, "Okay. So now I go to negotiate the deal with Cephalon." But it's still his deal. You can't drop some other little bird in the scientists' nest and ask them to treat it like it came out of one of their eggs. [laughter]

Hughes: Schering-Plough was one of the first big companies to move into biotech, and I can imagine that there were plusses and minuses to being one of the first. This was industrially unexplored technology, except on a very small scale if you count what Genentech was doing.

D'Andrade: There certainly would have been minuses if we hadn't succeeded with interferon. People would have said, "Well, that was a wasted effort, money, focus."

Development of Interferon

Hughes: Did you ever have your doubts?

D'Andrade: Yes. Well, not me, because by the time I came on board, Charles had already cloned the immature form of interferon. I had a lot of doubts that we were going to be able to develop it on the production side. There we got some people to take ownership. A scientist by the name of [Tattanahalli L.] Nagabhushan, who had really grown up in our development effort with the antibiotics, really took ownership of that development effort. If that had not happened, we could have gotten stalled simply trying to make interferon in commercial quantities that would assay out the way it needed to.

Hughes: I understood you just to say that you weren't particularly worried because the gene had been cloned, but it was a big worry on--

D'Andrade: The development side.

Hughes: Yes. Schering wasn't investing in Biogen just because it was doing good science. You were investing in it because this particular science was supposed to lead to a product.

D'Andrade: Well, I thought you meant, was I worried that the basic science wouldn't work.

Hughes: Well, that was a question, too, wasn't it?

D'Andrade: It was, but by the time I came, interferon had been cloned, and after I sat through enough of those scientific board meetings, I simply didn't have any concern. As a matter of fact, I was probably over-optimistic about what biotechnology would produce, and probably I'd call myself today over-optimistic at the time we acquired DNAX and over-optimistic for a lot of years after that. So, maybe I should have been worried, but I wasn't worried that we were on the wrong track from the basic science point of view. I don't know how anybody could have spent as much time as I did with people like Wally Gilbert, Charles Weissmann, and Phil Sharp, and not be convinced that they were going to be successful. They were just extraordinarily intelligent people, with more energy and drive and determination than most corporate executives have. Just extraordinary. So I was on board.

Now, the development side worried me a lot, and we worked very hard on it. My role was running the interferon task force. That's mostly where I laid my hammer, on the development side.

Hughes: That was particularly unknown territory, right?

D'Andrade: As I say, we agonized over glycosylation; we agonized over methionines, plus or minus; we agonized over containment issues; cost. We didn't know what it would cost to ferment large quantities. Yields. Our first estimate of the size of the plant we had to build for interferon was extraordinary. The cost was staggering. But we went ahead to start building that and got a very significant yield increase. I don't remember what it was about the process that produced that yield increase. It was at least a full order of magnitude. So we built a plant a tenth of the size of the one we had on the design table.

Hughes: The process was worked out in-house?

D'Andrade: Yes.

Potential Patent Litigation

Hughes: My understanding is, there was potential for a lengthy litigation between Roche and Schering-Plough over patents. Would you like to say a word about how that was settled?

D'Andrade: Roche had gotten a patent as a result of having been the first to purify natural interferon, I guess to a crystalline structure, and the [U.S.] Patent Office gave them a patent therefore on interferon *per se*. And we knew that on its face that patent would roof a patent we got, or expected Biogen to get, as a result of Weissmann's work in producing natural interferon via the cloning of the gene. We thought that we'd have a pretty good argument that the patent office should never have issued that patent to Roche for all the reasons patent lawyers think up why patents shouldn't be issued. There was also a question as to whether Weissmann would get the patent on human interferon produced by biotechnology, or Genentech/Roche.

It really came down to the lab books and who was the first to reduce to practice the production of a clone coding for interferon, and that ultimately came out in Weissmann's favor. I don't remember by how many days or weeks he beat [Sidney] Pestka by, but he did. That wasn't entirely clear to us how that would work out. I believed it was necessary to enter into a license agreement with Roche, and we talked to their people in Switzerland and talked to their people here and had lots of meetings.

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D'Andrade: I negotiated the settlement, and what I negotiated was essentially: "You go your way; we'll go our way, and any patents you get, you won't use against us, and any patents we get, we won't use against you." There was a reluctance on both sides, when it got really down to it, to try for more. We were splitting the pie in half, sort of saying, "We'll let you believe you discovered the product, and you'll let us believe we discovered the product." To get that result, I had to get Luciano together with Irwin Lennen, the president of Roche U.S., and after a couple of hours in Luciano's office, they came to an agreement that we just ought not to be fighting with each other over this.

So we entered into an agreement that had that basic effect. We also had to persuade Biogen, because Roche would be out there selling an interferon that Biogen was convinced they were going to get the patent on and wouldn't owe any royalties

and would be taking sales. Even if they'd pay the royalty, they'd be taking sales that we would probably be paying our royalty on. And Roche had to convince Genentech, which believed that they owned, or would come to own, the intellectual property. So there were a lot of people who didn't want to do the settlement.

Hughes: Did those patents set some precedents? The field was still forming in terms of intellectual property rights in biotechnology.

D'Andrade: The Weissmann patent was certainly a pioneer patent. It didn't set any precedents as that word would be meaningful to a patent attorney. I don't know what conclusions molecular biologists reached about how to go about their business if they wanted patents. I would guess it didn't teach many lessons there. There were people who said, "Well, you won't get a patent on this." Some people said, "You're not going to get a patent because it's obvious. It wasn't easy to do, but it was obvious." I think there were people who said, "The patent office really will accept that this science is going to lead to patentable products." But it took a long while for that interferon patent to issue, so I don't think Weissmann was anywhere near the first [to be awarded a patent in biotechnology?].

Hughes: Do you remember when the patent issued?

D'Andrade: It will expire in the U.S. in 2001, I believe, so seventeen years prior thereto.

Hughes: The Cohen-Boyer recombinant DNA patent issued in 1980.

D'Andrade: Cohen-Boyer was very early.

Clinical Application

Slater: Somewhere between the actual process of the basic science and scaling it up to a plant, there's also clinical application. That changed over time. Was that ever a source of major doubt or controversy?

D'Andrade: Yes. I thought that we would get some strong evidence of interferon's effectiveness as an antiviral or an anti-cancer agent rather quickly. Of course, we didn't. We put it in every clinical trial we could think to put it in, and we

weren't seeing anything dramatic. And we were seeing dose-limiting side effects. The flu-like symptoms surprised us--surprised me, certainly. You think, "Well, there's plenty of interferon pumping around in the body. We're just going to give this to people, and they're not going to have any reaction to it." But they did. And a whole lot of people just couldn't tolerate those flu-like symptoms. They were really very intolerable. So then people began to say, on the outside, on Wall Street, "Interferon's a failure. It doesn't do anything." Now that did worry us. That did begin to look then like we might come up looking foolish. We just kept at it.

We studied that product in everything and are still doing so. We just simply were persistent, and so we got some hits in hairy cell leukemia. We said, "Well, do the studies. Get the approval from the FDA. I don't care if there are only five patients. We're going to get this product on the market." And then Kaposi's sarcoma. It was really hard getting some of those other cancer indications--malignant melanoma. It took very large numbers of patients in clinical trials. For a while, it really looked like we had good results in bladder cancer, and it turned out that we didn't have good results.

You may know that in hepatitis C the response rate the first time you treat people with a course of interferon is--I probably have these numbers somewhat wrong but not too wrong--20 percent. Then six months after discontinuing therapy, half of that 20 percent relapsed and they had evidence of the virus again. So it just took a whole lot of patients, a whole lot of time. So we never have had any quick and easy clinical results with interferon, unlike erythropoietin.

We gave erythropoietin--even G-CSF [granulocyte-colony stimulating factor]--bang! The white cells went up, the red cells went up, pretty obvious, pretty quick, and not a whole lot of side effects. That's really a neat one, erythropoietin and G-CSF. We've struggled with interferon. We're still working hard on it. I was sure--I'm still sure--that it would work as a treatment for rhinovirus. [laughter]

Slater: Heard that before!

D'Andrade: The clinical data doesn't support me, but I know I'm right! [laughter]

III REGIONAL CHARACTERISTICS OF BIOTECHNOLOGY

Biotechnology Centers in the United States

Hughes: Well, let's switch to a broad view of this region. When you think of biotechnology in the New Jersey area and its interrelationships, what comes to mind?

D'Andrade: I have not, and do not, associate biotechnology with New Jersey. I associate pharmaceutical companies with New Jersey, but not biotechnology. I associate biotechnology with the Cambridge area, Palo Alto area, and that is really it. Some people tried to put some biotechnology into Denver. Some people tried in Houston.

Hughes: What about San Diego?

D'Andrade: San Diego, yes. I think we can almost take the Palo Alto circle and draw it down the coast to San Diego now. [laughter] But back in the early days, it was Cambridge in Boston, and Palo Alto, and not even San Diego at that time.

Hughes: Why was that?

D'Andrade: Well, where was Genetics Institute, where was Biogen, where was Amgen, where was Cetus, where was Genentech? Now Centocor had set up in Malvern, Pennsylvania, which nobody had ever heard of. But Centocor also went off the map in the sense of looking like it was going to be a successful biotech company. And in any event, Centocor was concentrating in monoclonal antibodies. If you were pursuing the Holy Grail of IL-2 or any of the other interleukins that you thought might cure cancer or any other disease, the people who--the cloning successes--of course there was Immunex up in Seattle, Washington. The guys who were cloning stuff and winning were Amgen, Genentech, Genetics Institute, and Immunex, I guess, in those days. There were biotech companies being started up by entrepreneurs in New

Jersey, including Wally [Walter] Steinberg, who worked out of Menlo Park, New Jersey and formed a whole lot of biotech companies.

Hughes: How early on?

D'Andrade: Very early on. He was one of the early founders of Human Genome Sciences, Vertex, and a whole lot of others that I can't think of now. So there was a lot of money and a lot of entrepreneurs in New Jersey, close enough to the pharmaceutical companies to know they'd have an opportunity if they set the company up to come and do business with us.

Hughes: Why didn't biotechnology work here to the degree that it did in the places you named?

D'Andrade: Well, I'm going to tell you this as if you didn't know it. Okay?

Hughes: Yes. [laughter]

Proximity to Universities

D'Andrade: It's the virtuous circle. The Biogen way of organizing things demonstrated that the people with the techniques to do this early cloning were in universities. They weren't in our laboratories. They weren't in Merck's laboratories. They weren't in Pfizer's laboratories. They weren't in Warner-Lambert's laboratories. You could have gone to every pharmaceutical company in New Jersey and you wouldn't have found a Wally Gilbert. Wally started out in life as a physicist. That's what he got his original Ph.D. in. He decided molecular biology was the place to be if he wanted to do something big in science. So those people were in universities. And you had the spontaneous event, [Robert] Swanson and [Herbert W.] Boyer getting together, and so of course that would be near one of these universities.

Swanson couldn't have gone to Boyer and said, "Let's set up a company in Denver." He was going to stay at Stanford [University of California, San Francisco]. And then you had postdocs coming out of places like Stanford and Harvard and MIT, and to the extent they're willing to work in private industry, they want to work for somebody like Boyer or [Arthur] Kornberg or Paul Berg or Sharp. So they're going to stay where those people are. Then when an entrepreneur wants to start up

a company, he's going to set it down where there are molecular biologists to hire from other biotech companies. If you're not specifically academically oriented and you want to be in this business, wouldn't you rather work for a company in Palo Alto than for a company in Denver? Because if you don't like your boss and you're in Palo Alto, you can get another job without having to take your kid out of school. I forget who was in Denver. It doesn't matter. But there was a biotech company, a serious one, in Denver.

The research link was critically important because molecular biologists with the skills to do that early work were only in the universities. This is an area where we were taking things that were worthy of publication in *Science*, *PNAS* [*Proceedings of the National Academy of Sciences*], *Nature*, that were the kinds of things that people could dream Nobel Prize around, and immediately moving them into a pharmaceutical company. As soon as Charles got his clone, it went into a thermos, got on a plane, and came over to our labs. This isn't the normal transition of things from academic environment to industry. It usually takes a longer period of time.

Maybe when it takes a longer period of time, it can be done by the chemists coming out of [Robert Burns] Woodward's lab. (Woodward was at Harvard, and the man in organic chemistry.) Then the chemist could even go to Switzerland and work for Roche in Basel, or could go to Merck and work in Rahway, and take his knowledge and use it at Merck. Merck didn't have to go sit on the doorstep of Woodward's lab. It didn't work that way. We had to be on the doorstep of Gilbert's lab, Boyer's lab, Berg's lab, Kornberg's lab. So the venture capitalists set the companies up on the doorsteps of those labs.

Venture Capital

Hughes: There were pots of venture capital, from what you said before.

D'Andrade: Yes. It worked out nicely that there were established venture capitalists in Boston and in San Francisco. But it wouldn't have mattered. The venture capitalists in New York would take their money and move it to Boston.

Hughes: Or here.

D'Andrade: Or here. That's not an issue for them at all.

Scientists and Big Pharma

- Hughes: Of course, another way that things could have been done, as a few companies tried to do, was to create their own in-house biotech venture.
- D'Andrade: Merck did. Well, that's not entirely true. Merck did not do deals outside. Merck said, and I believe this story, and I think probably it still reflects an opinion at Merck, "We're not interested in large molecules." I think Merck recognized the importance of molecular biology as a tool to understand the cellular system, to develop assays against which to screen small molecules. But that was the more classic hire-the-postdoc-out of-the-lab-of-the-guy-at-Harvard, whether it's Woodward or Gilbert; bring him in here, and we'll learn how to use that [technology] as a tool to do our traditional research. The people who were saying, "This is not our traditional research. We're doing this in part because it is a whole new source, a direct source, of therapeutic agents," couldn't wait to hire the seminal agents of transmission of knowledge into our organizations. That's why I wanted to buy DNAX as opposed to building that group up internally, which was the alternative that we discussed and argued about.
- "You can't," I said. "One, it takes too long to hire that many molecular biologists. Two, we can't hire molecular biologists of that quality." We were in Bloomfield. I said, "They won't go to work in Bloomfield."
- Hughes: Not only Bloomfield.
- D'Andrade: They wouldn't go to work at Rahway.
- Hughes: Yes, they wouldn't work for a large company. They wanted to stay in a quasi-academic environment.
- D'Andrade: They'd want to stay in that virtuous cycle. They'd want to be able to go to seminars at Stanford; they'd want to have beer with the guys who stayed in academia.
- Hughes: Wouldn't they be worried, too, about being in a corporate hierarchy?
- D'Andrade: Yes. They wanted to work for small companies. They wanted to stay near their friends. They wanted to stay near their mentors. They wanted to be where there were a whole lot of other people like them. But that virtuous cycle applies to why a lot of businesses are geographically clumped.

I think, in addition to the clumping that occurs because of the values of a virtuous cycle, that we can now say, "Well, why did they clump where they clumped?" It was because of this short or almost nonlinear transmission time from the labs--with the only people in the world with the talent to do it--to industry. Now in time, we were able to get postdocs from Berg and Kornberg and Boyer and Sharp and Leroy Hood, and get them into the Genentechs and the Amgens and Genetics Institutes. I forget the name of the guy, the scientist who founded Genetics Institute. He was kind of a competitor of Gilbert's at Harvard.

But you couldn't have gotten the people out of the university labs to come to work there if there wasn't somebody like that. They were suspicious, and rightly so, I think, of the Mercks and Pfizers and Schering-Ploughs because we had ordinary--well, I won't say "ordinary"--we had traditional organic chemists who, like Merck, believed in small molecules. They're probably right. I don't think the world of therapeutic agents has been overwhelmed by the large molecules, and the small molecules are still winning. Random screening [for new drug possibilities] is still winning. [laughter] It's remarkable.

Two Cultures

Hughes: Well, it seems to me you're talking about different cultures.

D'Andrade: Oh, we are.

Hughes: It also seems to me that you, in some of these instances, were the bridge person between these two cultures. You had to make the cultures mesh and they had to work collaboratively. On the other hand, wouldn't there be an impetus to keep the cultures distinct because they're useful in a functional way?

D'Andrade: Yes. There are values that can only be preserved by keeping them distinct, particularly in the more fragile organization, which is the start-up organization.

IV SCHERING-PLOUGH ALLIANCES WITH DNAX AND OTHER BIOTECHNOLOGY COMPANIES

Giving DNAX a Free Rein

D'Andrade: After we acquired DNAX, there was the normal desire of our people to help it in simple ways. There was the desire, of course, to try to turn it into a Schering-Plough, which was easier to resist because it was a bigger effort. We said, "No, we're going to leave them [DNAX] out there. They're going to have their own management. It's going to look like an academic organization. They're going to be allowed to hire postdocs. Those postdocs are going to be allowed to work mostly on their own projects. The scientists are going to be allowed a lot of time to work on their own projects." So those were big issues. They were fairly easy to handle.

Hughes: Why did Schering-Plough think that was the way to go?

D'Andrade: Well, we wanted to be able to track and retain and keep the enthusiasm of the kind of scientists that we believed demanded that kind of environment, and that kind of environment was the best culture in which to grow those kinds of organisms.

The little things were the hard ones to fight. The security people wanted the doors locked after six o'clock. They didn't understand that these people go home for dinner and then come back at nine o'clock and work in their labs until twelve o'clock. Or they shouldn't be able to bring their children in the building because it can't be secured. A guy would go home, come back in to check the experiment for twenty minutes, and he may bring his daughter back, or she may bring her daughter back. So the little things took fighting. But the belief that I had, and that Luciano agreed with, was that we had to allow DNAX to look as much like an academic laboratory as possible.

There was a lot of talk about, "Well, how are we going to get them to work on things we want them to work on?" There were two answers to that: first is the Arthur Kornberg answer, which was, "How the hell do you [at Schering-Plough] know what they ought to work on in the first place?"² [laughter] "Who's smart enough to figure that one out?" The second is, when it is clear enough what people ought to be working on, they will work on it. They will understand. Okay, Schering-Plough had said, "We've got to look at products of T-cells. We're not going to look largely at the products of B-cells. We're not interested. We're looking at products of T-cells." Even the postdocs. That'll be what the organization does. If you talk about it, people will be really interested and excited about your successes, and if you talk about something else, they'll be less interested because it's not what they're driving toward.

That's the [Alejandro] Zaffaroni view. The goals of the organization, if they're clearly understood by the people at the top of the organization, will come to co-opt the best people who work there because the best people will want to be successful in the terms of the goals that you've established. That, I think, has worked out pretty well.

Misjudging Product Development Time

Hughes: Did you, from the start, realize how much time there would be before you had a product?

D'Andrade: Absolutely not. I did not have any idea. I believed that within ten years of our acquisition of DNAX, we would have a cornucopia of cellular proteins that would signal other cells to do really great things--turn them off, turn them on--specifically in the field of autoimmune disease. Get at all the confusion the body has when it sets off its T-cell-produced regulators to attack cells. It just seemed to be obvious. Something is signaling those cells to go after it with gamma interferon, or IL-2, or all the other pro-inflammatory cytokines, and we'd be able to turn that off.

² For Kornberg's views on DNAX, see his oral history: Arthur Kornberg, *Biochemistry at Stanford, Biotechnology at DNAX*, an oral history conducted in 1997 by Sally Smith Hughes, Ph.D., Regional Oral History Office, The Bancroft Library, University of California, Berkeley; 1998. Also online: <http://www.lib.berkeley.edu/BANC/Biotech/>.

On the other hand, when it was a good idea to get after something, whether it was an infectious organism or cancerous cell growth, we could get those T-cells geared up to shoot out their stuff to attack that. It just seemed to be obvious. [laughter] All you've got to do is understand, which I thought we had all the tools to do, how those cells are signaling and being signaled, and we'd have the answer to all these autoimmune diseases. Ten years. It hasn't happened, and it's not happening. You'd have to be a scientist, which I'm not, and you'd have to probably be a pretty good one to know why it's not happening, other than to say that, "Well, it's a lot more complicated than we thought it was." They started out thinking in terms of lymphokines, and then they started talking in terms of cytokines, and now they're talking in terms of chemokines. It's a little bit like thinking there's nothing but atoms and then you find electrons, then you find quarks, and then you find quarks with color and quarks with charm. [laughter]

DNAX Contributions to Schering-Plough

Hughes: So where does this leave Schering-Plough in relationship to DNAX?

D'Andrade: Fundamentally, DNAX has been a great success for Schering-Plough. I said that I thought when I came to Schering-Plough that it had a traditional view of pharmaceutical research and wasn't courageous. The association with Biogen, the association with DNAX, the association with people like Arthur Kornberg, have subtly and not-so-subtly changed the calibration of the managers of Schering-Plough--myself, Luciano, [Richard] Kogan, and even the research management. So what used to look like a dangerous cliff edge doesn't look so dangerous any more. So they just more comfortably get out to the end of things. Not even molecular biology necessarily. I think it changed the appreciation, the value of intellectual rigor. Or another way to put it, really smart people are better to have than people who are just smart enough. I don't think we could have attracted some of the people we have attracted without the association with DNAX which gave us a credibility that, frankly, I don't think we had as a research organization in the early 1980s.

Interestingly enough, Schering did have it in the 1950s and 1960s with its steroid work and was on the cutting edge. It was where things were happening. It was also successful

with antibiotics, more serendipitously than I think the steroid work that we did. The steroid work that we did successfully was done by organic chemists really working on the leading edge.

Then we became successful in antibiotics in a more serendipitous way. Pop up out of the mud and you've got a great antibiotic. The chemists have less of a role in that and we began to put a lot of energy into looking for continued success in the antibiotic field. Probably the chemists were just seen as having a role and perhaps tweaking those compounds when we found them, whether in the mud or from a mold off a tree.

But whatever happened, I think by the early 1980s, Schering-Plough had just an ordinary research organization. I think that the fact that science had so much force in the biotechnology field was a wake-up call both to management and to the scientists. Then finally, on a more specific level, our understanding of biotechnology, or molecular biology of cell behavior and cell signaling, is making possible a lot of the assays and screens we're now using on the small molecules that we're getting from our own chemists and from outfits like Pharmacopeia, and the high through-put screening you can do. So we wouldn't be where we were if we hadn't done what we did in biotechnology. But the number of proteins as therapeutic agents *per se* in our catalogue right now--I imagined a lot more.

Hughes: If I can summarize what you're saying, the relationship with DNAX did pay off for Schering. It was just in a different way than you anticipated.

D'Andrade: Yes. There are therapeutic proteins out there, and we're now working on interleukin-10, which I think is a drug certainly for Crohn's disease and probably for rheumatoid arthritis. And there are some more. It's not just something where you crank the handle and find the gene that produces the protein that's going to turn off the attack on what we call rheumatoid arthritis. It turns out the antibodies do better than trying to find a protein. Anti-IL-2 probably will work as an agent, which down-regulates the production of pro-inflammatory cytokines like IL-2 and gamma interferon. But the monoclonal antibody route is pretty good. Just get an antibody to IL-2, give it to people for the treatment of arthritis, which is what Centocor just did; or an antibody that blocks the IL-2 receptor for the treatment of arthritis, which is what Immunex just got a product approved for.

Other Alliances in Biotechnology

Hughes: Can you look on the recent alliances between Schering and various biotechnology firms as in some way coming out of this experience with Biogen?

D'Andrade: Well, if it hadn't been for Biogen, we would have never been able to contemplate gene therapy. We just wouldn't have had the management which would have understood what it meant to try to replace a mutant or missing gene, and the possibilities of it. As a matter of fact, I think to some of us, it probably seemed a lot easier than it is. "Yeah, right. Why not? Give 'em a gene! Put it in an adenovirus. We can understand that. We put genes in organisms to get them to produce proteins. We'll put genes in viruses to get cells to take them up." So if we weren't in fact chock-full of people who do understand and think they understand the way the genes in a body help it or hurt it, gene therapy would have been too extreme for us. I think unless we'd had experience with the integration of DNAX, we would have perhaps been too cautious to believe we could integrate a Canji. We would have done a deal with Canji, but the idea of buying the whole outfit and running it from New Jersey might have seemed a bit of a stretch.

Our other agreements, if you look at what we've done recently, a lot of them are what I'll call tools and methods, whether it's Pharmacopeia or Incyte or Human Genome Sciences, or some of the others where what we are really after are their understanding of, say, a dominant gene in families which experience very high rates of high cholesterol, or very high rates of schizophrenia. That is the tool sort of use. Let's find a gene that we think accounts for this, and then maybe we can find some targets on that gene, and we'll target them with small molecules. There's hardly any company that I can think of that is using as many of the tools of biotechnology in drug discovery as we are. I'm sure Merck is. Probably Pfizer is. But I don't think anybody's using more.

Hughes: You've talked indirectly about personality, but could you say something in summary fashion about your perceptions of how individuals have made a difference in this new field of biotechnology?

D'Andrade: I don't have anything really to compare it against. Somebody like me is very lucky when they're there when a new field gets born the way this one was and see the people who make it happen and come to know them a little bit, whether they're extreme like Wally Gilbert, or they're very solid like Phil Sharp and

Paul Berg, or they're very powerful like Arthur Kornberg, very smart like Charles Weissmann. So it may be that any new field is a product of extraordinary minds, and it only is saying something pretty unextraordinary to say that the new field could not have bubbled up, sprung up, the way it did without these extraordinary personalities. But it's certainly the case in this field that there are just an awful lot of extraordinarily unusual people, whether it's Leroy Hood developing the sequencing capability, or Arthur Kornberg with his [DNA] polymerase work, or Paul Berg or Wally Gilbert.

In this field, or physics, or mathematics, it's extraordinary that extraordinary people come together at a moment when things are really about to pop. My guess is that the genes for creation of extraordinary people are pretty evenly distributed over time, and they're always out there, but when a field is about to pop, the really extraordinary people come at it.

Science seems to me sometimes to be a bit like a big sticker, trying to get it off of something. Well, you work a whole long time getting an edge. When you get an edge, you're careful, and you don't want to rip it. But there comes a point where you feel you can now really pull it! When you get that, the last 80 percent pulls. Well, I think in science, a whole lot of people are working, working, working, working, and one day somebody gets their finger on it, and they pull it, and then there it is. Wow! Then they really go for it.

There were some extraordinary people who got those edges. Kornberg was one of them. He only had an edge. He couldn't see that that was going to allow Berg and Boyer to do what they did. Even Berg and Boyer were still working on an edge. But then it allowed the Gilberts and the Weissmanns and the others to really make biotechnology a realizable way to get the products of human genes in large-scale quantities. So I would say the personalities were extraordinary and without them it wouldn't have happened. But I can't imagine that there wouldn't have been extraordinary personalities to gather around and help pull the cover off this piece of science. It's really a lot of fun when you're there, and you get to meet them and watch some of it happen.

Hughes: Yes, it was a unique position you were in.

V DIRECTOR, BIOTECHNOLOGY INDUSTRY ORGANIZATION AND
PREDECESSOR, 1981-1998

Joining the Board of Directors

Hughes: You were director of BIO [Biotechnology Industry Organization] from 1981 until this year. How did you become associated with BIO?

D'Andrade: When I moved to Schering-Plough and became involved with Biogen and interferon, I was asked to join the Industrial Biotechnology Association [IBA], which had been formed by several of the biotech companies not long before. I don't recall exactly which companies those were, but I think that they included Biogen, Genetics Institute, Cetus, Genentech, and perhaps Monsanto. I said that Schering-Plough would join if I could have a seat on the board. They agreed and created two classes of directors, one for the start-up biotech companies and the other for large companies. Bylaw assured that the biotech companies would always have a majority on the board.

The Organization's Mandate

Hughes: What was its original purpose?

D'Andrade: While I am not sure what the motivation of the founders of IBA were, I believe that a major consideration was the fear of biotechnology, particularly on an industrial scale, that was being fed by the press, abetted by many environmental/green groups and Jeremy Rifkin, an active and for a time successful opponent of almost everything we were doing. We had these problems at the national level, the state level, and even the community level. For instance, there was a lot of resistance in Cambridge, Massachusetts to the establishment of biotech

labs. So a lot of IBA's effort in those days was in working to convince the press and politicians that our critics were grossly exaggerating the risks and ignoring the potential significant benefits of biotechnology.

Hughes: Why did you become a director?

D'Andrade: I wanted to be a director because in my years at Ciba-Geigy I had been very active in the Pharmaceutical Manufacturer's Association [PMA], and believed that IBA could accomplish a great deal, but had to be sure not to adopt some of PMA's attitudes of arrogance and isolation.

Hughes: What were your goals for BIO?

D'Andrade: I thought the IBA could, by emphasizing its link to science, the future, and to America's entrepreneurial spirit, get politicians to see the industry as something that should be encouraged, nurtured, and supported. That the best way to avoid an adversarial relationship was to avoid an adversarial relationship.

Hughes: How did BIO change during the years you were director?

D'Andrade: I believe that we were successful and the "let us together move America ahead" approach is still the correct one for the industry. I also thought that it was important that IBA's staff not get so large as to develop its own institutional agenda. This too has been largely accomplished so that the major change has been in the size of the membership. That started with a merger between IBA and a trade association made up of the smaller companies called Association of Biotechnology Companies [ABC]. Discussions between IBA and ABC were opened up when I was IBA's chairman, although we were not able to get the merger done then.

Key Events in BIO's History

Hughes: What would you name as the key events in BIO's history?

D'Andrade: Other than the merger with ABA, I would comment on three other key events. The first was the hiring of Carl [B.] Feldbaum. Carl has brought to BIO all the qualities needed in his job and, most importantly, maturity. He is an adult and remains so even when dealing with someone behaving at the moment like a child, and believe me, in a trade association there are plenty

of those, as there are in Washington, D.C., many of whom he also has to work with.

The second event was the Clinton healthcare plan, which in dealing with on the Hill, BIO established itself as credible and as having a lot of support back home. The third event was the recent passage of FDA reform legislation. While that was a cooperative effort between PMA and BIO, without BIO it would not have gotten done. BIO went into those negotiations with a great deal of credibility with FDA because of BIO's years of interaction with FDA based upon its nonadversarial approach, and I think came out of the negotiations with even more credibility with the FDA.

D'Andrade's Resignation in 1998

Hughes: Why did you resign from the directorship this year? Do you retain an association with BIO? Have there been changes in BIO since you stepped down as director?

D'Andrade: BIO has adopted a rotation policy for its directors so that more members can get to sit on the board, and it became my turn to rotate off. I remain in touch with Carl Feldbaum and with what's going on in terms of issues. There don't seem to be any significant changes since I left the board.

Advice on Big Pharma-Biotech Interaction

Hughes: If you were giving advice to another pharmaceutical executive who wished to get into the field of biotechnology, what would that advice be?

D'Andrade: Well, if I were talking to a pharmaceutical company that was trying to figure out whether to get into the field of biotechnology, I'd probably just tell them they're too late. "Take a look at your company and figure out where your strengths are and concentrate on them. Then you're going to have to go out and work with Pharmacopeia or HGS [Human Genome Sciences] or somebody in connection with whatever that is you're strong at. But it's too late to become a biotechnology company/pharmaceutical company."

If somebody said, "Gee, all my guys jumped on the biotechnology bandwagon a decade ago, and they've been working hard at it, and we've got all these people doing all these

projects, and I'm just the new CEO and it's come to me, and I don't know whether that makes sense. What model should I follow? Should I follow a Schering-Plough model where you have a DNAX and you have a Canji and you have relationships with a lot of biotech companies and you're still pouring a lot of money into interferon and IL-10, and gene therapy? Or should I follow a Merck model where they seem to be concentrating more on traditional medicinal chemistry? And can you please tell me what the model is at Roche because I don't understand it." I would say, "If the people you have working at biotechnology are first-class people, then continue to provide them the resources to do what they're doing, because they're going to provide your whole organization with a lot of insights. Whatever you're doing to discover new drugs, the people who are doing that are going to need to understand the kinds of things that molecular biologists understand."

There was a time when there was an argument about whether pharmaceutical research was going to be taken over by molecular biologists or not and the organic chemists were just going to be shoved aside. Today at least, there's a discussion going on in my own mind about whether the organic chemists are now going to say, "Well, molecular biologists failed. Push them out and take over again." But I think that a pharmaceutical company has to be both a biological company and a chemical company. You've got to have a head of discovery research who, if you talk to the person about science and about drug discovery, you wouldn't be able to tell whether they were credentialed in a biological field or a chemistry field. They can talk like and think like a chemist, and they can talk and think like a biologist.

If the person asked me, "Well, does that mean that physicians ought to be put in the ascendancy, because they're biological but still understand medicinal chemistry?" I'd say, "No. That's not what I'm talking about."

Hughes: You want a scientist.

D'Andrade: You want the understanding of bench science, but it's got to be somebody who can wear the mind of both the chemist and the biologist.

Hughes: Do you want to say anything more?

D'Andrade: No.

Hughes: Thank you very much.

Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

REGIONAL CHARACTERISTICS OF BIOTECHNOLOGY IN THE UNITED STATES:
PERSPECTIVES OF THREE INDUSTRY INSIDERS

David P. Holveck

An Interview Conducted by
Sally Smith Hughes
in 1999

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Regional Oral History Office
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BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

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Occupation Arch Engineer Birthplace Pittsburgh Pa

Mother's full name Grace E. Holock

Occupation Assistant Treasurer Birthplace Allentown Pa
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Occupation House Maker Birthplace Phila Pa

Your children Lisa M. Holock , Jennifer C. Holock

Where did you grow up? Morrisville Pa (Bucks Co)

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Areas of expertise Medical Marketing, Biology
Management / Leadership

Other interests or activities Science, People - Golf

Organizations in which you are active BIO organization, Pa. Bio. Lab.

Board of Governors of the State System of Higher Education

SIGNATURE David P. Holock

DATE: 11/30/00

INTERVIEW WITH DAVID P. HOLVECK

Education and Early Career

[Date of Interview: February 2, 1999] ##¹

Pennsylvania Schooling

Hughes: Mr. Holveck, would you start with where you were born and educated?

Holveck: I was born very near to Bucks County, Pennsylvania, in Trenton, New Jersey, which is adjacent to eastern Pennsylvania. I was raised all of my formative years in that area and from there went to a state college in Chester County.

Hughes: What was your ambition?

Holveck: I was one of those late bloomers, coming out of high school. If it wasn't for the tenacity of my father saying that I had to continue my education, I probably would have opted to do something else. But he pushed me into going for one more year after high school to a local prep school right here in the area, Malvern Preparatory School. It was through the influence of the Augustinians and some of the other elements at Malvern Prep that I saw the light and went on to West Chester [University]. I think I was always interested in life sciences, so I took more of a life-science curriculum as a preparatory move to be a physical therapist. I had a degree in education--health and physical education--and along with this, a science background. I wanted to go into physical therapy.

¹## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

Medical Products Divisions of Abbott Laboratories and
Corning Glass

Holveck: The Vietnam War was on, so when I graduated, I went into the service for almost three years. I was in the navy and served as an enlisted man at sea. When I got out, I was married, and I'd had a child, and I had to get on to earning a living, so what went on the shelf was further education to be a physical therapist. I got into sales with a local company that was based on supplying blood components to hospitals and using plasmaphoresis technology. I did that for nine months, then joined Abbott Laboratories. At that point, it was called the Radiopharmaceutical Division of Abbott; today, it is the Diagnostic Division.

Computerized Tomography at General Electric

Holveck: I was there for about two and a half years, then went to Corning Medical, which is a division of Corning Glass Works. They were really just entering into reagent diagnostics. They had been in life science--more support equipment, pH meters, blood-gas instruments--but now they were going into reagents and diagnostic tests and such. I was there for five years; moved from sales to inside marketing and business; and then was recruited to go to General Electric Medical [G.E.]. General Electric Medical was really a transition, to go from small diagnostics to large capital equipment, such as CT [computerized tomography]. It was during a period of time when that was a technology that was really revolutionizing the imaging business. That was in 1978.

Hughes: Why did G.E. want you?

Holveck: That's a question I also asked. I think it was for a little bit of my track record in business, a little bit of a recruiter doing homework in finding names, a combination of those, and I got the interview. I think what made it work was, the individual who was hiring came out of Abbott Laboratories and had an understanding of my diagnostic background, albeit it was not a background of heavy or large equipment; it was reagent. But he saw my understanding of that particular field, and I got the nod, which was in terms of career development very beneficial. It was certainly the master's degree in business that I don't have but I'd gotten as a result of working in G.E. for five years. It was a period of time that was an exciting technical run in the industry, and being a part of it and seeing the action as it

related to G.E., I learned a lot. There was a lot of technology and business skills that I learned.

Centocor

Recruitment as Vice President of Marketing and Sales, 1983

Holveck: In 1983, I got a call from Centocor. Centocor was founded by Michael Wall, an entrepreneur who has started many businesses, and our current chairman, Hubert Schumacher. Hubert and I knew each other when we were at Corning, worked well and built certain aspects of the product line. When I went off to G.E., he left a year later and joined Michael Wall and started Centocor. Centocor was founded in 1979. In 1983, they called me. It was at a point of time where they had some products, and they were looking for someone to take on the business and marketing.

I had evolved through G.E. from the CT business; G.E. asked me to take up another venture, a business called digital X-ray [imaging systems], which I did. The next opportunity was for MRI [magnetic resonance imaging]. But I wanted to go into a company that gave me broader latitudes. And knowing Hubert and knowing the field from the reagent and biotechnology side, Centocor seemed like a good opportunity. I was from this eastern Pennsylvania area, and I was living at that point, with G.E., out in Wisconsin. My parents were getting older, so it made a lot of sense to come in and see if I did learn anything at G.E. and put it into play with a smaller company.

Hughes: It was quite a risk that you were taking, was it not?

Holveck: I didn't see it as a risk. I always felt there was a greater risk staying in Wisconsin and working at G.E. in the sense that if you didn't work at G.E., you didn't work. I always felt that I'd rather be at a more diverse location. I liked the East Coast. The Midwest was fine, but for professional reasons I wanted to be able to do more, to have more say. As you move up in any large company, it becomes a little bit more bureaucratic and change is harder to effect. Most people will tell you, you either make a change at five years, or you're a lifer. So the five-year benchmark was about the time when a number of professional opportunities could be best realized. And I was at an age--in the mid-thirties--that I felt that if I was going to try something, this would be the point to try it. If I failed, I

would be on the East Coast, and there were certainly many companies I could move to. So I joined Centocor in June of 1983.

Monoclonal Antibody-based Diagnostics

Hughes: What did you find?

Holveck: I found a very, very small company, maybe forty-five or fifty people. It basically had one product, which was a version of hepatitis testing that was already on the market, and some early prospects for cancer diagnostics. A pretty raw force of people.

Hughes: Did you have any particular feeling about a monoclonal antibody-based company?

Holveck: Well, I felt that I knew the monoclonal technology since that was really evolving when I was at Corning in the late 1970s. Most of the diagnostics that I had worked with at that point were polyclonal, and certainly I knew all of the headaches and problems of polyclonal. So the technology and the evolution of the technology, both diagnostic and therapeutic, was known to me and intriguing. As a technical platform, I understood it and believed in it. The opportunity to play in that field and build an organization would give me the latitude to do what I wanted to do. So for nine years, from 1983 until 1992, I ran and built the diagnostic business. It was a highly profitable business with a good steady growth, and we built it up to its high point of about forty-eight million dollars with a 25 percent operating margin. It was highly profitable, it was global, and we networked our products--all of the major diagnostic instrumentation.

Hughes: Now, you had a lot of competition, did you not?

Holveck: Well, I think competition in diagnostics is pretty heavy, but in fact, we never really pursued the hepatitis. That was highly competitive and a field that we were very briefly in; we got out. What we did make our name in was cancer diagnostics, an area that was just emerging in terms of having good antibodies for cancer diagnostics. We found ourselves in a lead role with some unique product opportunities. That led us to having relationships with Abbott Laboratories and Hoffmann-La Roche, which gave us more critical mass and support and allowed us to fund other products after the first two tests. We had a test for ovarian cancer and we had a test for pancreatic cancer. Then we evolved a test for

breast cancer, and then GI [gastrointestinal] cancer and lung cancer.

Hughes: You were first in the field?

Holveck: Yes. We were first in the field with those types of tests and continued to lead the field with those. We got an early foothold. Over time, the tests became standard care; they were recognized by clinicians as "the" standard test. Because of the marketing strategy of networking with all of the major suppliers, we insulated ourselves from competition because we were the suppliers of the reagents, and they were looking for ways of adding tests to their instrumentation.

Partnering

Hughes: I'm not a business person, but to partner with larger companies seems an obvious way to go for a young company. Why were you unique in taking that approach?

Holveck: There are a lot of elements that drive companies. Ego is a big part of it, ownership, and the vision of being a self-standing, independent company. Moving from a partner relation to an independent is not the first thought that one has. There is the belief, especially when you're talking about a company that is founded on technology and unique technology, that if you have the better mouse trap, the world will beat a path to your door. So all of that, I think, plays into it.

There was a company that was founded under the same technical platform as we were. It's called Hybritech. That was out on the West Coast. Hybritech did take an alternate path. They forward-integrated their business and built a sales force and instrumentation.

Hughes: Quickly?

Holveck: Fairly quickly. If you were to look at their history and Centocor's history, they pretty much follow in a path, except we did more partnering--in fact, all partnering--and they did technology, evolution, and testing, but did a forward integration with a sales force and instrumentation. They ran head on into Abbott Laboratories. Abbott was--is today still--the force in diagnostics. It got to the point where Hybritech couldn't compete. They eventually were sold to Eli Lilly. Eli Lilly bought the company, not so much for the diagnostic side but for

the technology platform, and wanted to employ it in therapeutics and eventually was unable to really develop it. The culture and the entrepreneurial spirit was lost; when the big company came in, they were never quite able to continue the flame.

Hughes: Did this partnering approach predate your arrival at Centocor?

Holveck: Yes. When the company was formed, Michael Wall envisioned the ability to develop unique antibodies and out-source the reagents to people who could further develop them for either diagnostics or therapeutics. We would be a development house of antibodies and essentially a reagent supplier. I think that was his initial concept. We started to take more control of the development and the clinical study, so we owned more of what I'll call the development side than I think Michael would have originally envisioned, but we kept the out-sourcing of commercialization. And we did a lot of what we call market development. We did trials, and we positioned it from the marketplace and worked with a partner on how to market it. But in actual delivery to the customer and maintaining the customer in the field or in the global market and putting the reagents on the instruments, that was the partner's job. We got royalty streams off of that.

Co-founder Michael Wall

Hughes: What was the financial history of Centocor prior to your arrival in 1983? What got Centocor off the ground?

Holveck: Well, what got Centocor off the ground was Michael Wall's reputation as a very superior venture capitalist. He started well over fifteen businesses.

Hughes: Mainly in this general area?

Holveck: Not really. He's an engineer by education and training. I think he's been in all types of businesses. He's truly an entrepreneur. I don't think he's limited to technology. He sees opportunity and looks for ways to draft onto that opportunity and create value in that opportunity. He's been in the computer industry; he's been in the clothing and design industry; he's been in the life sciences in the latter part of his career. He's open and he's just a pure entrepreneur and his track record is sterling.

Hughes: He saw the potential of Centocor?

Holveck: He saw the potential with the technology of the antibody. His reputation allowed him to get eight million dollars of seed money right out of the box to get started. Centocor was founded in 1979, and then in 1982 they went public and raised another sixteen million dollars on the back of some of the work they had done.

Hughes: By 1982, there were a number of other companies founded on the platform of monoclonals.

Holveck: That's right.

Hughes: Why would one invest in Centocor?

Holveck: I think most of the companies that started found themselves invested in technology and putting their money into the enrichment of their technology and funding themselves, or bringing money into the company through contract research. That was something we never did. It was one of Wall's laws: we would not do contract research. We put our money in products. I think a lot of the early companies got themselves so tied into contracts that they diluted themselves to never really bringing a product forward. What differentiated Centocor was its ability to create products. There are some basic founding principles that we never veered off of. Even today, we don't do contract research. We basically focus only on products.

Forward Integration

Hughes: Is forward integration part of Centocor's strategy now that you're a bit further along in your history?

Holveck: Yes, we have forward integrated. All aspects of the business model are now completely forward integrated in the sense of development research, manufacturing, marketing, selling. We have our own sales force. Nineteen ninety-nine is our twentieth year. As a twenty-year-old adult, you're able to start to think "independence" and "self-sufficiency." That's where Centocor is right now.

Hughes: But if I understand you right, that was not always the plan.

Holveck: Right.

Hughes: Some companies have forward integration as a goal, right from the very start.

Holveck: It was not our plan. Our plan was founded as being producers of reagents. We evolved into product development and fully integrated into that side of it, using partners. Then, in the mid-1980s, we decided to take the technology platform and apply it for therapeutics. It was really in that period of time that we also started to see ourselves as forward integrating and bringing a complete business model together around the therapeutic focus. That therapeutic focus was using antibodies to treat sepsis, septic shock. Hence, the chapter in our history, the Centoxin era, was formed. And from 1986 to 1992, we essentially worked on that vision and dream of being a fully independent biopharmaceutical company, essentially built around the success of Centoxin. It didn't happen.

Centoxin

Hughes: What happened? [laughter] For the record, tell the story.

Holveck: It did not happen. It was flawed in a number of ways. It would be easy for me to say it was flawed on a strategy, but it really was flawed on culture. It was flawed on people. As anything that starts to evolve with a number of people, it's organization, and it's the inner workings and the community spirit that's developed. What happened was that the originating culture got fragmented.

In the mid-1980s, when we decided to go to therapeutics, we needed to raise money. We discussed it within the company, and it was felt that our endeavor at that particular point was diagnostics, and it didn't lend well. We had to create an organization that was more in tune with pharmaceuticals, and we went out and brought in managers--leadership, if you would--that came out of the pharmaceutical industry. And it was really a breach in the culture. It was now an organization that was starting to fire itself and create its long-term plan off of an established pharmaceutical vision. At that particular point, the industry was pretty set in believing what the formula for success was. And it was thinking big, spending a lot of money, creating a lot of infrastructure.

The managers that came in from the industry didn't have an understanding of the start-up, of the bootstrap mentality. There was a degree of arrogance, and that fractured the culture. I think it attracted a group of people that were not really entrepreneurs; they were good business people, but relied heavily on a more specific organizational design, not an open

architectural design that you would find in more opened, entrepreneurial businesses. Over time--from the mid-1980s to 1992--you saw two businesses at Centocor: there was the diagnostic business, which was pretty much of the founding culture; and there was the pharmaceutical business, which was, as I say, nurtured out of big pharma. Of course, when the product did not pass FDA [Food and Drug Administration] review, many things started to occur. But I think what really occurred was there was such a negative bias and pressure created by this pharma culture, or this alternative culture, that there was very little support for it. So there was a backlash. The end result was that the board decided to move that management team out. That's when I was asked to take over.

Holveck and the Re-creation of Centocor

Hughes: What did they see in you?

Holveck: Well, I guess, there were a number of things. Certainly a familiarity, for one. Obviously, I was one of the early players, although not a founder. I think there was a track record; the diagnostic business was highly successful and profitable. I think there was a trust. Obviously, when the company hit the road it hit, I was a known entity within the employee base. To stem the tide of people leaving and losing faith, I brought that to the ballpark. So it was a combination of reasons.

Hughes: What did you do to save what was, essentially, a sinking ship?

Holveck: Clear, direct action, I think, was probably the mainstay of the strategy. It was to shut down completely any semblance of the hope of, dream of, continuing Centoxin. It was over. Then it was just shut off. We didn't let it linger. There was a clear assessment of what technical strengths we had and what other opportunities we had. That assessment led us to move forward with the cash and the help and the resources of the diagnostic business to bring that next product up.

Hughes: That was ReoPro?

Eli Lilly as Partner

Holveck: Right. We also were able to get the interest of Eli Lilly to come in early and partner with us in that venture.

Hughes: That must have taken some doing.

Holveck: To give you a little bit of the finer stroke, when Centoxin failed in 1992, there was an opportunity to continue the product in Europe. It was approved in Europe; it just did not get approved in the United States. In 1992 until January of 1993, we did elect to study one more time the clinical usefulness of the product, with a trial in the United States. I think we all thought, and Lilly thought, that stepping in at this point, albeit a little risky--but ReoPro did have an approval in Europe --that it probably was approvable in the United States. So, yes, on their part, it was a little bit of a risk, but I think what they saw was an existing product in Europe, potential, and another product coming. And for an equity stake and a little cash--fifty million dollars in equity and fifty in cash--it was worthy of a venture.

So, no doubt, it was one of those events. If you talk about the re-creation of Centocor, you'd have to put that right up there in the sense of getting that moral support. Obviously, in January of 1993, the second trial did not work. As I said, it was at that point that we just shut it all down and liquidated and got out of it. But Lilly stayed, because they did have the rights to the next product, and we worked on that. Hence, by 1994, we had secured approval for that product and introduced it in 1995. That got us back on track.

Corporate Culture

Hughes: Now, you spoke about the conflict in culture in regard to Centoxin. Was one of your aims, when you became president and CEO, to do something specific about restoring the biotech culture?

Holveck: Yes. I think what happened was that the employees became disenfranchised. Companies will always try to put some kind of tangible mark as to why that happens. Technology is a good reason. But, as good as technology is, it's only enabled by people. I really have felt all along that if you get people on your side--you get them engaged; you get them involved--you can

overcome a lot of issues. That's what we really went back to, getting the employee into the driver's seat, engaged, understanding. We spent a lot of time in facilitating platforms and communicating and making sure that they understood everything that we were doing, why we were doing it. Any question, no matter how big or small, was addressed. To the point where we stemmed the tide of people leaving, we really were able to capture the people and their belief in the company. We really secured and built back the passion because they understood the vision, and they understood the object of our efforts and felt that they were part of it. Many jobs at that particular time weren't all that plentiful. But even if they were, they didn't give you that much insight into the goings-on. That's a big part of what allowed us to hold people and reignite the energy level and passion.

Hughes: So it was a people problem--or a people solution.

ReoPro

Hughes: One thing you might have thought of doing was to go back to the tried-and-true area of diagnostics and just concentrate on diagnostics. But you didn't.

Holveck: Right. We didn't. I think the industry was evolving the diagnostics for a number of reasons that really prevented that thinking. Although I was a part of the diagnostics business, I too saw the future. The future was being heavily impacted by AIDS. AIDS as a disease was wreaking havoc in health care. It was a tremendous cost burden to health care. It really fragmented the diagnostic pie. Even though we may have proclaimed a war on cancer, it was really AIDS that was consuming our dollars. And diagnostics was heavily impacted. The economic pie in health care did not increase. It was really cut differently, and most of the diagnostic dollars were going towards AIDS diagnostics. Consider, now, we're talking about the mid-eighties. We were looking for better diagnostic tools to be able to cut out and identify early. So money and the diagnostic tools were being heavily invested in. What wasn't being invested in is future cancer diagnostics. It was really a matter of time; that was not our field. I felt that we could exploit it and run it pretty hard, but the best opportunity was to focus on what we now know as ReoPro. That's what we put our money on.

Hughes: That meant developing new capabilities within the company and also different sorts of partners.

Holveck: You're talking about in therapeutics?

Hughes: Yes, in therapeutics as opposed to diagnostics.

Holveck: Yes. A lot of what we were able to retrieve after Centoxin was a hidden element. I think many companies refer to it as a skunk works. These are the things that go on because there is the passion, the insight, and even the shroud that's created because everybody's focused on a bigger project. What we had going in ReoPro was a skunk-works project, although it was legitimized. But there was far more critical mass and thinking going on, and it was headed by an individual who was a young, aspiring research cardiologist by the name of Harlan Weisman. It was really his passion. While everybody was running around and thinking the world was going to be saved, and we were going to be some gigantic, big company overnight because of Centoxin, he was laboring with his crew on ReoPro. Obviously, when the bubble broke and we looked around, Harlan had put together and knitted together a real, solid technology achievement with the antibody and some clinical studies that looked quite promising.

Going back to the people and the culture, we were able to meld that and bring that together and really expedite that program and move it forward. When you ask me if we had to create a new infrastructure--not really. Not really, because we had the inner workings from the cardiology group that he had put together. The diagnostics was still independent and making money. Then we had Lilly who was giving us some guidance and insight.

Slater: How did your previous negative experience with big pharma shape how you went about developing your relationship with a partner like Lilly? What did you want from them? Had you set up some kind of firewall?

Holveck: No. I think that survival instincts were taking over then. My comments about big pharma were really around that particular age and era. I think the Lilly organization was open. It would be hard to generalize and say, "All big pharma is bad." I think that Lilly did have a very open attitude. I didn't find them at all risk averse. I think that we felt comfortable enough. At the same time, we knew our backs were to the wall. I think it was the blending, if you would, of our attitudes and their tolerance. Maybe it's the Midwest-Indiana tolerance that fits well with our humbling experience, and we were able to learn how to work together. It was a really good working relationship. Well, it still is. It was not a heavy-handed relationship.

Now, a different partner could have come off differently. Certainly, Lilly wasn't the only one that was competing at the period of time when we were looking at partners, so we looked at other partners. But Lilly, to their credit, was probably the most aggressive and then put the best deal on the table. As you look back at the history of Centocor, there are events that occurred and could have broken a different way, and we wouldn't be here today. You can't explain it. But the Lilly aggression and choice worked out very well for us.

Regional Characteristics of Biotechnology²

Importance of Locale

Hughes: Well, let's leave Centocor for a minute and go to your perceptions of regional characteristics. What is there about this area that either promotes or holds back biotechnology?

Holveck: Locale is important. As I mentioned earlier, when I was with G.E., I found being out in Wisconsin somewhat restrictive. I think that the East Coast, which is a hotbed for health care, at the university and academic settings or in the industry itself, is a very good critical mass to draw from. The location also allows you to work with the money men up in New York, if you're evolving a business. I think it also allows you to work with the policy makers in health care. Health care is heavily regulated, and being near Washington is very helpful. From a global aspect, being able to commute to Europe is also facilitated by being here on the East Coast. It's five to six hours by plane.

The other hotbed of biotech is on the West Coast. It's been successful, so I don't know that we could say geography has been limiting. But I think location on the West Coast is more of a challenge, given the time differences, given the ability to get in and out of Washington or to New York, and such. It's just a little bit more restrictive, but you work around those. I find that the East Coast and this particular region, the university settings, and the critical mass in the industry are very helpful.

² This section moved for better topicality.

Entrepreneurialism

- Hughes: What about the entrepreneurial spirit, willingness to take risks and sink money and effort into a new venture?
- Holveck: Well, I think that is probably the difference between the East and West Coast. I think that there's a greater element of risk-taking on the West Coast. There is a larger and more aggressive venture-capital basis on the West Coast than you find here on the East Coast.
- Hughes: Why is that?
- Holveck: It stems from the electronics and computer technology that evolved there. I think the formative businesses, the early entrepreneurial spirit, were fostered with the early electronics wave that still is very strong out on the West Coast. It's that early money that really allowed a lot of venture capital people and firms to be put together on that early wealth that was created. That allowed that entrepreneurial spirit to be fueled as biotechnology started to come around. It's not that entrepreneurialism doesn't exist here; it's just that it's never been at the same level. I think venture capital is a little bit more conservative, a little bit more risk-averse, not as open here.
- Hughes: Has that been a problem for Centocor?
- Holveck: Yes, it has been a problem. Venture capitalists underwriting businesses, if you just look at the sheer number, you're going to find more on the West Coast than here. It's not that it's absent, but it's more difficult. I think the individual states on the East Coast haven't been as aggressive because they didn't really need to be aggressive. There's a fairly strong industry base here. A lot of states support programs putting the venture-capital programs together, which are there to create jobs and create growth industries. As I said, there's a fair amount of very substantial, well-heeled industries here, so there wasn't even a state motivation to spew money or support money for growth. I think the region here, although strong in terms of academics and industry, has been a little bit light on venture capital and the ability to spawn start-up businesses. Now, that's changing.

Research Universities and Technology Transfer

Hughes: You mentioned in passing the importance to the region of research universities. Do they continue to play a role?

Holveck: Well, yes. A little less today because the model's a little different. But in that particular time period, universities were not as sophisticated as they are today in tech transfer. To a large extent, universities didn't have tech transfer offices. They basically relied on a network--and a loose network--of researchers, publishers, entrepreneurs, and businesses working directly with the researchers, either through funding and then out-licensing and in-licensing. It was on an informal basis. Yes, the early elements that make up some of our product portfolio today were founded on Michael Wall and Hubert Schumacher building a relationship with researchers in universities and obtaining from the university a license--a royalty agreement and a development agreement--which allowed us to bring products forward.

Now, today you can't get into a lab and talk to a researcher without having a clearance from the tech transfer office. The empowerment of the researcher to do a deal has been taken away, and it all goes through the tech transfer office. It's a more competitive arena than what we knew of back in the early days. The network that Michael and Hubert had created comprised the areas that we cultivated and allowed us to move forward. We built on that early research and further developed it from the standpoint of what the company does best. I would consider us a very good developer with very good understandings of research. But we don't have what we call the big "R." We have big "D" and little "r." We rely on the academics.

Other Factors

Hughes: What other aspects of this area have played into the way Centocor and biotech in this region have developed?

Holveck: Biotech has evolved slower than people would have liked. What we've all found is that developing products for human consumption is heavily regulated and fraught with many problems. The basis under which companies really have to evolve in this long, protracted development time is money and people. The proximity to New York has been helpful in that we can get up and get in front of the money men, if you would--the big investment bankers,

the investors, and the supporters. That played well. I do think that the ability to get good, trained people allowed us to continue to get skill sets where we needed them.

The ability to move up the chain and build a competitive and critical mass of technology, money, and people worked well here. Not only from that aspect, but the elements that I think this industry has struggled with is learning the regulatory environment. It's a highly regulated industry, and there are no shortcuts. You have to do it one way. That's been a difficult lesson for the industry to learn. It is an industry that was founded on entrepreneurs and academics. To subject them to the harsh regulatory rules has been difficult. We fell on our own sword because we felt that there were shortcuts because we had better technology, and regulators would look at it differently. But they look at it the same way. If you don't do it their way, you go to the penalty box. I think that that's really been a struggle. But over time we've gone through this evolution where the sooner you learn those rules of the game--the ability to stay focused and nurture the people side of the equation--the sooner you get there.

Hughes: You now have that expertise in-house, whereas maybe at an earlier stage you were relying on your various partners, or ignoring it entirely in the case of Centoxin.

Holveck: Yes. Well, there was a period of time where we ignored it. Then there was a period when we brought it in and I guess used it as a box that we checked off. But I don't think we lived by it. Then from the accumulation of enough scar tissue, we understood that you have to live by it, and we integrated it into the culture. And from where we sit today, yes, it's absolutely woven into the culture.

State of Pennsylvania and Biotechnology

Ben Franklin Partnership

Hughes: There are various business-related organizations in Pennsylvania. Please comment as to their relevance to the development of the biotechnology industry. One of them is the Ben Franklin Partnership.

Holveck: Well, Ben Franklin Partnership is a state-sponsored way of getting dollars into the hands of entrepreneurs. The problem is

that it's fairly limited. I think the major grant that they can give is a couple hundred thousand dollars. Now, that's not chump change, but it's not going to fuel a blast furnace. It'll get you going. I think, going back to my earlier statement, that the network wasn't there to take the next step, be it the VCs [venture capitalists]. But the Ben Franklin Partnership was one of the early state-supported programs that allowed the state to funnel some venture money into starting businesses. It exists today. But it's capped as to the amount of money it can put in. I really don't know the amount, but it's pretty limited.

Hughes: It played no role in Centocor's history?

Holveck: No, Ben Franklin didn't play a role.

The Biotechnology Network of Technology 21

Hughes: You were--maybe still are--chair of the Biotech Network segment of [Pennsylvania Governor] Tom Ridge's Technology 21?

Holveck: Yes. Tech 21 was a program that Governor Ridge put together early in his term to collectively energize the thinking at the state level on how to build and put a more forward and aggressive face on the state to attract businesses and develop. It was made up of a number of key technologies, of which biotech was one. Yes, I was a participant there. To his credit, the governor did create a forum that allowed the exchange of ideas and looked at all elements of current programs and how future programs could be put into play to make the state more competitive in attracting businesses and helping the state legislators see how things come together. It's worked out pretty well.

Hughes: Have there been some technical results?

Holveck: Yes. I don't know that I could articulate it well, but we had this strange tax that taxed people in the way computer businesses and computer technology was used.

Hughes: Thank you for your comments.

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REGIONAL CHARACTERISTICS OF BIOTECHNOLOGY IN THE UNITED STATES:
PERSPECTIVES OF THREE INDUSTRY INSIDERS

Edward E. Penhoet

An Interview Conducted by
Sally Smith Hughes
in 1998

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

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Organizations in which you are active _____

SIGNATURE



DATE:

11/9/00

INTERVIEW WITH EDWARD PENHOET

I FAMILY BACKGROUND AND EDUCATION

[Interview 1: September 11, 1998] ##¹

Parents

Hughes: Please start with your family background and education.

Penhoet: That is an important part of regionalism, because my family background is regional, in the sense that I was born in Oakland, California. I spent virtually my whole life in the Bay Area, with some exceptions we can get to later. So I'm a Californian in many senses of that word.

My father, Etienne Penhoet, was an immigrant from France, but my mother, Helene Dangles was born in San Francisco, and her parents were immigrants also from France who came in 1890 or something like that. My mother was born in 1908. I was born in 1940. My [maternal] grandparents had been here for fifty years before I was born, but my father had just been here for just twelve years, because he came in '28.

Nevertheless, immigrant background or no, I grew up in the California culture. My father was a businessman and amateur artist, and my mother was a musician. Actually, she was a founding member of the Oakland Symphony in the thirties. She taught violin and piano. So I came from a household with a more artistic bent, full of music and art. My father did business because he had to earn a living, but he was not a businessman, at least not a businessman at heart. I got my early exposure to business by working in the hardware store which he owned when I was a child.

¹## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

The Postwar California Context

Penhoet: I grew up in an era in California when technology was part of the grand plan for the future. Even when I was a child in the late forties and early fifties, we always felt that in many ways California was the leading edge. This was the era when nuclear energy was going to solve all our problems. The Pacific Gas and Electric Company held many demonstrations on the power of the atom and how it was going to solve all our problems. I'm talking now about the early fifties.

Being born in 1940, I obviously was a child during the war years. But my formative years, that I can remember at least, started at the end of the war, the span from '45 to '58. I was growing up in this environment. And those were the days when technology was going to solve everything. We built all the stupid freeways like the Embarcadero Freeway in San Francisco, and nuclear power was going to run everything, and microwaves were being invented. People came to our school--I went to a public school in Oakland, Fremont High School--and fried eggs without any heat, so that was the first microwave demonstration. And stereo music was also introduced in our school. So technology was the thing. Everybody was involved in technology-related matters. Also, Sputnik was put in space by the Russians in 1957, and that started a big technological race between the United States and Russia.

Technology was just part of growing up in this region. This is my perspective on it, of course; I'm not sure everybody felt the same way. It was a time of tremendous optimism in America, but particularly in this region--growth, expansion, going to the moon, all of these things were bubbling up in that era.

Childhood and Adolescence

Technological Orientation

Penhoet: I was very fortunate to go to a school in Oakland at a time when the science and math training was outstanding, and when there were resources in the community like the Chabot Observatory in Oakland to help stimulate interest in science. So by the time I started thinking about going to college, I was pretty firmly hooked into the technology world. I had some aptitude in math

and science. Schools also had probably more effective counseling in those days, so I was encouraged in this direction.

Choosing a University

Penhoet: I went off to college in a very technological mode, thinking at first I was going to go into engineering, partly because I didn't really have much exposure to the field as a whole. So engineering sounded like it must be the right kind of area to head into. I applied to several schools and decided in the end to go to Stanford. As much as anything else, it was a reaction to growing up here, in the sense that I was always a little bit contrary. There was an assumption that if you went to school in Oakland and were a good student, you were going to go to Berkeley. So since that was what everybody else was going to do, that's not what I was going to do. So I went to Stanford instead, intending to go into an engineering curriculum.

Hughes: Stanford had a strong engineering program?

Penhoet: Yes. I had conversations with a lot of people: Should I go to Berkeley, should I go to Stanford? Those were the two choices I made at the time, probably a reflection of the parochialism of the area. I didn't think about going to Yale or Harvard. I thought about going to Caltech. I sought advice from people, asking: "What do you think of this, what do you think of that school?" They all had outstanding engineering schools at the time, and so no one gave me strong guidance one way or the other from a programmatic point of view. But from a cultural point of view, wanting to be doing something different than what everybody else was doing, I decided to go to Stanford.

Early Interest in Engineering

Penhoet: I was interested in electrical engineering at the time, in part because as a kid I was interested in music, and I combined my interest in music and technology by building high fidelity music systems. There was no stereo in those days, but you could buy kits to make amplifiers and all these things, so I'd have lots of fun making these things and hooking them up and driving my mother and my sisters crazy with loud music in the house at an early age.

Before I went to Stanford, I worked for PG&E for six months, because we graduated from school in those days every six months. I graduated in February 1958. I had six months to kill, so I worked for PG&E as a file clerk, believe it or not. You've been at Chiron many times, Sally: in the PG&E yard which is right next door to Chiron, that's the first job I ever had. So, it's a small world. But I also had a friend in the neighborhood, a man who was in the power engineering business. I used to go and talk to him about his business and got interested in it from that point of view.

Outdoor Activities

Penhoet: In those days, we lived in a sort of fringe area of Oakland; my parents lived near Mills College. That was a newly developed part of Oakland, and we could hike in the hills and go into the parks. We essentially lived on the edge of the city. We had a lot of energy, so we did a lot of hiking.

Hughes: "We" is your family?

Penhoet: Yes, and my friends in the neighborhood. We had a neighborhood group. I think part of the western mentality is activity, outdoor activity. We probably shot too many birds, so we were not much good for the local bird population, but we were out there every day doing something.

Stanford Undergraduate, 1958-1963

Switching to Biology

Penhoet: I went to Stanford in engineering. But I wasn't there very long before I decided I didn't want to go into engineering. Believe it or not, one of the catalyzing events occurred during orientation week when our class was divided into the engineers and everybody else. I first went to the engineering group, and then I realized they were all male, and they all carried slide rules, and I thought, Do I want to spend four years with this group? I don't think so. So I went back to the other group, and the rest is history, as they say. [laughter] That's actually a true story. So I became a biology major, with an interest in going to medical school.

Hughes: How did that happen?

Penhoet: Well, there was nobody in my family who was a scientist. There's probably generally a barrier to going into science. Unless you have some concept of what a scientist does, it's a little bit mysterious. If you go to school thinking you're training yourself for an occupation, which at some level most students do, science is a little bit abstract. People pick engineering as a profession, medicine as a profession, and it would be a logical step from biology to go into medicine.

Research in Clifford Grobstein's Laboratory, 1962-1963

Penhoet: I spent several years as a pre-med student. I wasn't a great student. I did very well in some things; I flunked other things. I had lots of distractions in my life when I was an undergraduate. But when I was a junior--no, maybe I was a senior--I had done quite well in an embryology class taught by Clifford Grobstein. When the class was over, he asked me if I would be interested to learn about research by working in his lab, as an undergraduate student.

Hughes: Was that commonly done at Stanford, to work as an undergraduate in somebody's lab?

Penhoet: Yes. We're going to get back to this, because it's a very important point. So I agreed to do this; in fact, I eagerly went to do it, because I got interested in embryology in this class.

Assisting William J. Rutter

Penhoet: I started working in Grobstein's lab when Bill Rutter was at Stanford on sabbatical from Illinois. That was Bill's first experience on the West Coast. Although Bill grew up in Utah, he came to Stanford to spend this year [1962-1963].²

² Rutter was born and grew up in Malad, Idaho, until the age of fifteen. For information on his life and contributions, see: William J. Rutter, *The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California*, San Francisco, volume 1, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1998.

Grobstein said to me, "Well, maybe a good way for you to learn science is to help this guy here on sabbatical, so why don't I just assign you to him, and you can work with him and learn science at the same time." I did that together with Judy Oppenheimer, a first-year graduate student, who ended up working with Bill and me. So the three of us formed this motley crew to begin to study pancreas differentiation. That's when Bill got interested in the pancreas. It was my experience working with Bill that got me truly interested in pursuing a career in science.

Hughes: He didn't object to having a relatively untutored person assigned to him?

Penhoet: Well, Bill would take any help he could get. I was a pair of hands, as far as he was concerned. He probably figured out that I was competent to run an assay--I was trainable. I didn't do any heavy intellectual lifting at that point in time. [laughs] I was checking the mice and helping do tissue culture--I was actually pretty good at that--and at running the assays.

Hughes: He hadn't done much biological work up until this point, had he?

Penhoet: Well, no, most of his work prior to this was in enzyme mechanisms, and it was more purely biochemical. He'd ground up some animals, I'm sure.

Hughes: He had done research with chickens--galactose metabolism.

Penhoet: Pigeons' livers.

Hughes: I am thinking that he had some learning to do at Stanford as well.

Penhoet: Oh, for sure, yes.

Marriage and Carmel, California, 1963-1964

Penhoet: After we spent that year together, Bill went back to Illinois, and I went to live in Carmel for a year and worked in an automobile dealership owned by my father-in-law, William Stahl.

Hughes: When did you marry?

Penhoet: Did I get married before Bill came to Stanford? About the time he was there, I guess. My wife, Camille Stahl Penhoet, was also a Stanford student; we were at Stanford together.

I took a year off and went to Carmel, and Bill went back to Illinois. Then we mutually decided that I should come to Illinois for graduate school [1964-1965].

The Stanford Context

Experiential Education in the United States

Penhoet: The Stanford experience for me was extremely important. To understand this region's entrepreneurial spirit, you have to really understand some special stuff at Stanford. It's a quality which I'm not sure anybody can fully describe. Stanford has been successful in turning out entrepreneurs in some multiple of any other place.

Hughes: With the possible exception of MIT, would you say?

Penhoet: Yes, that's probably right. But Stanford was maybe greater than MIT overall. It's not totally clear what is responsible for this. You asked me, was it common for undergraduates to work in labs. You may know, Sally, that there was a sea change in education which occurred in this country 150 years ago, from learning by reading to learning by doing. The old academic model was pure study of books, learning what was in the books, becoming an "educated man" or woman, but it wasn't at all mixed up with any experiential concept of learning.

That changed 150 years ago with what used to be called natural science. People who were natural scientists encompassed everything from astronomy to biology and everything in between. But these people did much more experimental work, somewhat after [Louis] Agassiz who was a very important figure who worked in Massachusetts. A group of colleges got started based on the practical applications of learning. The first was Cornell, and then Indiana, and then Stanford. These are all very highly related to one another. I don't know if you've ever been to Cornell or Indiana. They have the same school colors; they have a lot of the same campus characteristics, because they were all fundamentally started by the same group which went from one to the other to the other. Cornell was funded by Ezra Cornell, who

was basically a farmer, a very successful one, who really wanted to found an institution with a practical bent.

Undergraduate Research at Stanford

Penhoet: I think that tradition of involvement in learning rather than simply reading as a learning experience is something that follows and has roots in that long tradition that's still evident at Stanford today, and certainly evident when I was there. So it wasn't unusual for undergraduates to be involved in research. On the contrary, it was quite ordinary for students to be involved in research. There was no organization to it, though; you had to take initiative, but there were quite a few undergraduates who got involved.

Stanford Self-confidence

Penhoet: The other thing about Stanford, and it's a little hard to describe exactly, is that there's a certain self-confidence among Stanford people. Those less-kind-to-Stanford describe it as something more pejorative, like cocky or arrogant. On the other hand, that arrogance--let's call it arrogance for the moment--leads in a way to the notion, Well, hell, I can do it. If anybody can do it, I can do it. So that attitude--arrogance is probably too harsh a word--that "can-do" attitude, and the confidence to just go out and do things, is somehow a collective phenomenon in the Stanford psyche. Although there are kids from a lot of different backgrounds there, they all think they're pretty swell people.

Stanford has had a deliberate policy for many years of trying to find well-rounded students. They like people who did athletics and who were officers of their class or their student body and who worked on the student newspaper and were good students and had a broad skill set. As opposed to Harvard, for example, which has always looked for the very special people, the Yo-Yo Ma's of the world who are absolutely number one in cello, and it doesn't matter whether they can do anything else or not. So it's a different admissions philosophy. But for whatever reason, I think it's a general phenomenon among Stanford people that they're more self-confident than the average person on the street.

Hughes: Seems to me there's another thread too, and that's the practical application of knowledge. There is quite a tradition, going back before World War II, of Stanford having ties with industry. Stanford Research Institute and numerous companies have been generated at Stanford.

Penhoet: Yes. And some of that had already occurred before I got to Stanford. All these factors were obviously at work for me. I of course didn't realize it at the time; I was just going through one day to another, trying to get along in that environment. But they were all there.

Expansion of Biological Science at Stanford

Penhoet: The other thing which happened at Stanford, which was crucial and obviously will come out in many of these analyses, is the arrival of Paul Berg and Arthur Kornberg and Josh Lederberg. This was like three Moseses coming off the mountain to Stanford, because this was the era of DNA. DNA was magic at the time. So although they were in the medical school and never had anything directly to do with undergraduates in the biology department, their aura was very large.

Hughes: Were you aware of them?

Penhoet: Sure, absolutely.

Hughes: Even as an undergraduate?

Penhoet: Oh, for sure.

Arthur [Kornberg] used to give campus lectures on the replication of DNA and related activities.³ It was a heady time in that sense. Anybody interested in biology had to be aware of his presence. Also, the medical school had [1959] moved down to Palo Alto [from San Francisco] just before I got there, so there was all this expansion on campus. It was again this same sort of expansive time: Moses and his two brothers show up telling us what's in the Rosetta Stone for life, and the campus is building, and the medical school is going up. So you just assumed life was

³ For more on the Kornberg enterprise at Stanford, see: Arthur Kornberg, *Biochemistry at Stanford, Biotechnology at DNAX*, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1998.

just going to keep going this way, and that was an underlying element at the time that influenced many of us who were there.

Stanford Faculty in the Biological Sciences

Penhoet: I think the other thing is: Grobstein was already extremely well known, head of the biology department, later became dean of the medical school at UC San Diego, et cetera. Charlie Yanofsky was down the hall, in the basement of this old building. Don Kennedy, who later became president of Stanford, had his lab around the corner.

As an undergraduate student, I felt like I was part of this group. I could discuss; I could make my points. Nobody said, "Well, you're just a lowly undergraduate; keep your mouth shut and listen to the great gods of the earth speak." So I was there as an undergraduate having coffee with Don Kennedy in the morning, discussing whatever he was up to. And I don't think my experience was unique in that regard. People respected undergraduates there. You weren't treated like a second-class citizen just because you were young.

The Psychology of Youth

Penhoet: I think that's also an aspect of the psychology of Stanford, but it may be generally in this area, because I experienced the same thing in Berkeley when I came. There's a culture of the young in California, probably sometimes misplaced. Nevertheless, young people here get a much earlier shot at being a peer than they do in many societies. In the German academic system, the Herr Professor, you get to be a professor when you're sixty-five, and until then, you're respectful of whoever is the boss, and you do pretty much what he says. Here, in my experience, people for the most part are respected as individuals and age doesn't matter a whole lot. We don't have an ageist society; if anything, maybe it's in the other direction. Youth is revered in our California society. So all those factors played a part.

Pioneer Spirit

Penhoet: I actually believe that Stanford is a tremendously powerful influence on the whole region. Not to say there aren't many other powerful influences as well, but this is sort of cultural--well, you'll find out when you talk to Dr. [Horace A.] Barker.⁴ He was at Stanford too as a student, obviously much earlier. He's ninety, so he was there thirty years before I was. He'll tell you stories about collecting species of plants all over the West. They just got in the car in the summer and off they went. People weren't plagued by insecurities.

Hughes: Well, the pioneer spirit.

Penhoet: Yes, it is the pioneer spirit. It almost sounds trite to talk about it, but it's really a very real concept, and it still exists, I mean, the pioneering of biotechnology and computers around here. So it's a different pioneering, but it's the same consciousness.

Everybody in California is an immigrant, whether they came from Massachusetts, or Brittany as my father did, they're people who are restless, looking for something new and wanting to go to the place where it's happening. There aren't many places like that where even the people who are not immigrants to America are still immigrants to California.

Graduate Student, University of Illinois, 1964-1965 ##

The Rutter School of Biochemistry

Penhoet: So then I went to Illinois to work with Bill.

Hughes: What was the motivation there? Was it the project itself--pancreatic differentiation--or was it Bill?

Penhoet: Oh, it was Bill. Of course, the two were inseparable at the time. I got my taste of science, if you will, by working with Bill on the problem of pancreas differentiation, so I was obviously interested in the field. It's a chicken-and-egg

⁴ The interviewer was about to begin an oral history with Dr. Barker, a biochemist at Berkeley.

problem. Would I have gotten interested in the pancreas if it wasn't for Bill? Well, yes, maybe, because I was in that lab and because I had an interest in embryology, kindled by this teacher Grobstein, not by Bill. But once I got in the lab, then the experience of working with Bill was commingled with the science, so there's no easy way to say whether it was the personality or the project. In fact, I didn't work on pancreas differentiation when I went to his lab. I did for a while, but I switched to another project.

I was absolutely, totally at least twenty feet under the surface of the water in Illinois, because Bill was in the chemistry department, and I was a biology major at Stanford. In order to get a degree, a Ph.D. in biochemistry at the University of Illinois, you had to be a competent chemist.

Hughes: Did you realize all that when you were making the decision to move?

Penhoet: Well, no. It was a binary decision. I'd do whatever it took to get approved for a Ph.D., but I might still be there if Bill hadn't moved to the University of Washington [1965-1968].

Hughes: So you didn't go to Illinois to become a biochemist.

Penhoet: No, I just wanted to go to graduate school and work with Bill. [tape interruption] I went to the Rutter school of biochemistry; wherever he was hanging out was okay by me. The fact that it was in Illinois was incidental.

Getting Serious about Academics

Penhoet: The year in Illinois was super important for me. As I told you, I wasn't a great student at Stanford; in fact, many times, I wasn't even a good student at Stanford. But I was faced with the reality in Illinois that I was going to have to become a good chemist. Otherwise, I wasn't going to get a degree. My spotty record at Stanford probably wouldn't have ordinarily qualified me to be admitted to Illinois. I didn't know it at the time; I just called Bill and said, "Hey, Bill, I'd like to come. See what you can do." Frankly, I'm sure Bill had to go through hell to get me in. Because Illinois was--still is, but at that time particularly was--one of the two or three best chemistry departments in the world. So this is how naive I was: I tell Bill I want to come, see what you can do. And of course, he got

me in. But I'm sure he had to go plead and scream and pound on some tables to get me in.

Once I was there, first of all, I couldn't let Bill down. But second of all, it was clear to me that my background was only marginally suited for a biochemistry degree. And maybe it was one of the reasons, actually, that Bill wanted to leave there too, because Bill's interests had become more biological.

Hughes: Yes, he said that in his oral history.

Penhoet: The Bill I knew was less a chemist and more a biologist. A biochemist, but with an emphasis on "bio." But Bill of old was a chemist doing biology or biochemistry, and that was the nature of that department at the time.

It was probably the most important year in my education. I got all this other stuff from being at Stanford, but I essentially got religion about academics at Illinois, because I had no choice. It was a very rigorous program. You had to pass exams in all these areas. I had to retake some absolutely freshman stuff that I had sneaked through Stanford without having to confront. So I had to take more basic courses in math, in organic chemistry, starting physical chemistry, et cetera. Those were things that I had been able to gloss over as a biology major at Stanford, but there was no glossing over those things at Illinois.

But fortunately, I did well in Illinois. I would have gotten a degree from there sooner or later, but it would have been more work than the way it ended up. It was an important year because of the content and because of the seriousness of purpose in this place. This wasn't fooling around anymore. Although Bill was able to get me in, he couldn't keep me in; I had to keep myself in once I got there. But it worked out; it worked out just fine.

Research on Aldolases

Penhoet: I did some experiments in pancreas differentiation when I first got there. But Bill had a residual interest in a group of enzymes called aldolases, enzymes he had investigated for many years. There were some nagging questions about aldolases in the brain that weren't clear from the studies Bill had been doing. Bill had done a lot of work on muscle aldolase and then determined there was a different kind of aldolase in the liver.

The properties of the liver enzyme and the muscle enzyme were quite different. Brains had enzymes which seemed to be in between the two, so it wasn't clear whether this was due to a mixture of the muscle and liver kinds, or whether something else unusual was going on in the brain. Bill was intrigued by this problem and thought it would be a good way for me to cut my teeth on doing some more rigorous biochemistry than what we had been doing in the pancreas. So I started on that program and that turned into a thesis for me.

Hughes: And the brain aldolase was different?

Penhoet: Yes. It turned out it was a new enzyme that had been undiscovered. In the process of doing that work, it became evident that the proposed structure of the enzyme was wrong, as then determined largely by Howard Schachman on this campus. So we did some experiments to prove that was the case, and that became my thesis.

Graduate Student, University of Washington, 1965-1968

Another Move

Penhoet: We didn't stay in Illinois long. I didn't push Bill forward just to solve my problems, that's for sure. But Bill had been there already a decade by then; I think he got a taste for doing things in another environment while he was at Stanford. So it wasn't long after I arrived in Illinois that it became clear to all of us in the lab that Bill had itchy feet and was thinking about moving somewhere. There were a lot of bets in the lab about where Bill would go, and one of the guys in the lab--I won't name him--got to be very good at reading Bill's mail, so we were kept up to date about where Bill would likely end up.

Hughes: You assumed that wherever he went, you would go?

Penhoet: Oh, it never occurred to me that I wouldn't. Or anybody else in the lab. Everybody went with Bill. Bill engendered a lot of loyalty. That's one of his great strengths. Finally, Bill decided to go to Washington, so we all went.

The Research Context

Penhoet: It was a great time in Bill's lab. The University of Washington was a great place to work.

Hughes: Why was that?

Penhoet: Well, partly because there were interesting people around in the department and in the school. We were in the School of Medicine in Seattle; it's a very long building. You could throw a bowling ball from one end to the other and it would probably take an hour to get there. It's all along the canal that separates Lake Washington from Lake Union. The building is extremely long, and we were at the very end. It was called the J wing, J because there was A, B, C, D, E, F, G, H, I, J, right? So it was this big long building attached to the medical school.

Biochemical analysis and medicine were just starting to recognize each other as valuable at that point in time. So there were collaborations with other people in the medical school. There was a good genetics department downstairs. There were two professors who later won the Nobel Prize for their work on how enzymes are controlled by covalent modification (phosphorylation). That's Ed Krebs and Ed Fischer, the two Eds. They were downstairs from us. They worked together; they were a team. So there was great faculty. It was a better home for me than a chemistry department, in the sense that there was a lot more biology around and interest in those subjects.

Hans Neurath

Penhoet: In retrospect, it was a great place to work because it was managed like a business. [laughs]

Hughes: Was it?

Penhoet: Well, there was a person named Hans Neurath, a very famous protein chemist, who was the chairman. He's probably the reason Bill left, but he's also the reason why it was such a great place. The place had a terrific stockroom; it had beautifully well-maintained laboratories; it was clean, orderly; it was a fabulous place to do work. But it got carried away.

One of the guys in our lab was a slothful person, and the chairman of the department told him to get his hair cut. This is

in an academic department! He forbade us to wear shorts to work during the week. So this department was regimented. I'm sure it's one of the things that Bill rankled at. On the other hand, unfortunately, fascism gets the trains to run on time. I wouldn't claim that Hans is a fascist, but you know what I mean. It was a very tight ship. And for that reason, you could really get a lot of work done in that place, because you didn't have to mess around with the infrastructure. It was there and it was extremely well done.

It was a very productive time in Bill's lab, so I think everybody in the lab felt that excitement of discovery, because the work was going so well.

Robert Roeder and RNA Polymerase Research

Hughes: It was the RNA polymerase period, wasn't it?

Penhoet: Right. Bob [Robert G.] Roeder, who is the best known of Bill's graduate students in the scientific community, was a graduate student at the same time I was with Bill. He started at Illinois at the same time I did, and he moved to Washington with the lab. He's the one who discovered three forms of RNA polymerase, although it was Bill's idea.

Hughes: That there should be three?

Penhoet: Yes. But Bob did the experiments. Bill worked in the lab when I was at Stanford with him; that was in '62-'63. I'm not sure he ever worked in the lab again. So Bill had the ideas. He did an occasional experiment, and everybody would run for the hills. [laughs] He showed up with his pipette. But in general, he provided stimulation and inspiration and a lot of the ideas, but he didn't get involved in the experiments themselves.

Hughes: You mean he didn't have golden hands?

Penhoet: No, I can't say that. But he didn't want to waste his time. He probably was wise in the sense that he had more ideas than he could conceivably carry out with his two hands, so he was better off to get other people to do the work.

Hughes: He was relatively young to give up bench work, wasn't he?

Penhoet: Oh, different people do it different ways. But yes, probably. Let's see, Bill is seventy-one now, so he was born in '27--

Hughes: No, he was born in '28.

Penhoet: That's what you think. [laughter] So he was thirty-five when he was at Stanford, and he was working in the lab then. That's probably fairly typical. Oh, you're right, he was born in '28.

Hughes: That's the date on his CV.

Penhoet: Right. There's some controversy about when Bill was actually born, like everything else about him. Most of the other faculty members didn't work in the lab. It's a rare circumstance, and these days even more rare. With all the time you have to spend writing grants and all the rest of the stuff, it's tough.

Anyway, Bob Roeder was in the lab at the time, and Bob has had a truly distinguished career in science. He hasn't won a Nobel Prize yet, but it is very likely that he will at some point.

The Rutter Laboratory

Hughes: Was it a big lab, along the lines of the one Dr. Rutter eventually founded at UCSF?

Penhoet: Probably about the same size. Not as big as the biggest he had at UCSF, but there were probably fifteen of us working in the lab. Twelve or fifteen, some number like that. Probably at the biggest, Bill had twenty people at UCSF. That's a big group.

Hughes: Was fifteen a big group for Washington?

Penhoet: No, the men that won the Nobel Prize, Krebs and Fischer, had big labs, about the same size. Hans Neurath had a lab which was about the same size. It wasn't unusual. But certainly it was an active group.

II GROUNDWORK FOR THE BIOTECHNOLOGY INDUSTRY

Work Ethic

The Rutter Example

Penhoet: It was there certainly that I established some lifelong working habits. First of all, Bill has always worked like three people. That was true when we were at Stanford. I'd come in to help him in the middle of the night, or Saturday, Sunday, whenever it was, and he was always there. He literally just lived in the lab when he was doing experiments with his own two hands. And this is really an important issue: the work ethic that Bill drove everything around him. It was routine for all of us to work every day in Seattle. We didn't complain about it. (Oh, occasionally people complained some, I suppose.)

There was always a sense of urgency around Bill. I can remember every time we would go to federation meetings [Federation of American Societies for Experimental Biology], which in those days everybody went to, everybody was up all night the night before making slides and doing experiments, because you had to have the absolutely latest data before you went to these things. Did it make any difference if you stopped two weeks before and made your slides? Probably not. But it was never good enough for Bill.

So this work ethic that Bill developed affected all of us. I'm sure not everybody has stayed with that kind of work ethic throughout their life, and at times in my own life I've worked less or more. I'm not as devoted to work as Bill is, but few people are. I think he's generally done it in a positive way--by example. He's not somebody who goes home and watches TV and then says, "You stay and work in this lab for me." I mean, he's there, working. So this work ethic was firmly established at that time.

There were good people in the lab. The pancreas problem really started to blossom at that time, so people generally were working on that, although the two people who became best known in the lab at the time, Bob Roeder and myself, neither of us worked on pancreas differentiation. We each had our own projects.

Diffusion of the Work Ethic: UCSF and the Biotechnology Industry

Penhoet: But talking again about what defines the culture of this area, it's this work ethic. So when Bill went to UCSF, he took with him, as you would expect, his work ethic. That became the work ethic of UCSF. I've never known a place in which people worked so hard, and I think it's the main reason it's been successful. I don't think the raw talent of that group of people at UCSF in the seventies was any greater than any other place. I respect them all tremendously; that's not the point. They were a somewhat above-average group of scientists who were way above average in terms of productivity, in large part because everybody in the place worked seven days a week, eighteen hours a day. And that still exists today to some degree.

That work ethic has permeated the biotech industry in the Bay Area. It really is the UCSF work ethic which has in one sense made these groups successful. It went to Genentech; they work that way. It went to Chiron; we work that way. It certainly in the early days of biotechnology was one of the distinguishing characteristics at Chiron. Now it's a different kind of an organization, but almost everybody who visited us then made the same comment: "You sense the energy when you walk into this place." I think that's more due to Bill than any other single thing. Bill wasn't at Chiron for the first ten years; he was at Chiron once in a while. He was mostly at UCSF. But still, it was Pablo [Valenzuela] and I, who had both trained with Bill, who brought that sense of urgency and hard work to the enterprise.

Hughes: Was that work ethic less true of an Amgen or a Biogen or any of the other early biotech companies? Or was that a pervasive feature of start-up companies in general?

Penhoet: It's a matter of degree. It probably was true of all those companies. People in science generally work hard. But I think it was probably taken to another level around here by this example at UCSF. The key guys at Genentech I know worked that way.

Competitiveness

Penhoet: Also, the sense of competition, direct competition, is something that also is a characteristic of Bill that has rubbed off on a lot of people. I'm not a very competitive person compared to Bill, but Bill loves competition, any kind. He just loves to compete. It's just fun for him. And I think he's affected a lot of people that way. So that's an important aspect of all of this.

Integration of Biochemistry and Medicine

Penhoet: I think the move to the University of Washington was a crucial move for Bill in the sense that it started this whole era of the integration of biochemistry and medicine, which was [later] fully developed at UCSF. The other reason that UCSF was so powerfully involved in the early days of biotechnology was because it was pregnant with people who were really interested in gene structure and gene function. So once Herb [W. Boyer] and Stan [N. Cohen] had done the cloning experiments, their application to medicine went whoosht, just like that, like wildfire through UCSF. Because the place was ready to do it.

Venture Capital

Penhoet: To some degree, what has happened in the Bay Area was some blend of this continuing influence of Stanford, which in a way is almost more cultural than scientific, combined with this almost pre-programmed--pregnant is the right word--situation at UCSF. And the other thing which was crucial around here was venture capital, because it was already developed. So when biotechnology came along, entrepreneurs didn't have to wait for venture capital to happen, because it was already here. There was already an association of venture capitalists. You'd buy thick books with the names of the venture capital firms and what kinds of things they did. It was relatively straightforward to get venture capital funding.

Hughes: As of the foundation of Chiron, circa 1981?

Penhoet: Well, even before that. Bob Swanson was a venture capitalist.

- Hughes: Right. I meant in terms of having references available; if you wanted a venture capitalist, it was like looking in a phone book.
- Penhoet: They were by '81. In '76 there were fewer venture capitalists, but Bob was one of them. He started Genentech. Venture capital in this region got its start with Silicon Valley, and most of the [earlier] investments had been made in computer-related technology.
- Hughes: The venture capitalists had not only been successful, but successful with investments in high tech. Didn't that help when you were looking for money for Chiron?
- Penhoet: Sure. No question about it.
- Hughes: There was a track record.
- Penhoet: Yes. And that's why, relative to many other areas, it was easy to do here, because they were all three here: the Stanford experience, the UCSF explosion of knowledge in this area, and then the ready availability--"ready" in quotes--of capital, all within twenty minutes of each other.

III UCSF

Rutter's Department of Biochemistry and Biophysics

- Penhoet: Bill went to UCSF with a scheme to deliberately recruit a whole bunch of people who were interested in the same things he was interested in; essentially to create a macro-lab, Rutter lab, where he had no direct control over these people. But he knew that if he hired the right people, they would all as a critical mass advance the field that he was interested in, which was the genetics of development, and gene function and expression.
- Hughes: In higher organisms. He made quite a point of that in his oral history. What he wanted to do was distinct from what had been done. Studies of gene function, et cetera, had been done mainly with prokaryotes.
- Penhoet: Yes. So this convergence of interests at UCSF was not an accident. Bill had a deliberate plan of whom he wanted to recruit to fill out this macro-group of Bill Rutter's. He won't admit that.
- Hughes: He admitted it indirectly. As you probably know, he turned down UCSF's offer probably three times. The way he told it to me in the oral history was, when he learned that there was a significant number of empty FTEs [full-time equivalent positions], he realized that he could recruit the people that he wanted.
- Penhoet: That's exactly what was attractive to him about the UCSF offer.
- Hughes: At that point, as he tells it now, he changed his mind, and he accepted the chairmanship.
- Penhoet: Yes. It was the opportunity to build this macro-group that I'm sure motivated him to come to UCSF.

More on Bob Roeder

Penhoet: In the meantime, I'd gone to [the University of California] San Diego [1969-1971]. I left his lab before he moved, so I never went to UCSF with Bill. Some of the people that were in his lab moved twice. I don't remember, who would that have been? Not many. Most of them had finished before Bill left. He left a year after I went. I don't think Bob Roeder went to UCSF. He probably finished just before Bill left. Maybe nobody moved twice.

Hughes: I never heard him mention Roeder in the context of UCSF.

Penhoet: No, Bob probably got his degree before Bill went to UCSF. He's the person who's at Rockefeller now who is very famous for his RNA polymerase work. He must have left at the same time Bill did. And then he and Bill became competitors.

Hughes: Oh, did they?

Penhoet: Oh, sure. In the seventies, Bob and Bill were both working on RNA polymerase, and Bill was competing with Bob, so they had a decade where they were still friends, but friendly competitors. But nevertheless, serious competitors.

Penhoet's Sabbatical at UCSF, 1978 ##Learning Recombinant DNA Technology

Penhoet: To some degree I'm an observer of UCSF. I've never worked there. I did spend a sabbatical year at UCSF, in 1978. I went over there to learn recombinant DNA technology, because Berkeley was quite far behind UCSF in this technology.

Hughes: Why did you want to learn recombinant DNA technology?

Penhoet: Well, it was clear to me this was the future, so I had to learn to do it.

Hughes: What made you think it was the future?

Penhoet: Well, because sequencing, first of all, was invented just about that time, so the ability to sequence DNA opened up tremendous possibilities to define genes and proteins. I was working in the

virology field and in the growth factor field here [UC Berkeley] at the time, and the application of this technology to infectious disease and to studying differentiation was obvious.

Hughes: Had you picked up an interest in virology in San Diego?

Penhoet: Yes. That's where I started virology. So for me it was clear, if you wanted to have the most powerful tools to understand viruses, you had to become involved in rDNA [recombinant DNA]. So I recognized, maybe not as soon as other people in the field but shortly thereafter, that this was the way of the future.

Hughes: It wasn't because you were talking back and forth with William Rutter?

Penhoet: No, in fact, Bill and I didn't spend much time together at all during that period of time. He was very busy building the department and the school. We saw each other socially on occasion. He asked me to be the best man in his wedding to Bonnie. And Gordon Tomkins was there [at UCSF]. I used to go over and visit people at UCSF. But there wasn't a lot of dialogue between Berkeley and UCSF in those days.

Hughes: So you came to the realization about the importance of recombinant DNA technology on your own?

Penhoet: Yes.

Hughes: It wasn't because you were in touch with a group that knew its importance?

Penhoet: No, I didn't discuss it with Bill. Frankly, Bill wasn't a big proponent of recombinant DNA technology himself for a couple of years.

Hughes: Why was that?

Penhoet: Well, he was busy doing other things. Some people in his lab were very frustrated that he didn't move into the field more quickly than he did, because to some degree, Howard Goodman and even John Baxter were more quick to jump on it than Bill's lab was. And in the middle seventies, Bill had a tough time in his lab. Because he was spending so much of his time building, working in the school, there were people in his lab who were very unhappy about the way the lab was going. Once Bill got into recombinant DNA, of course he got into it with a vengeance. But I didn't go talk to Bill about recombinant DNA.

Brian McCarthy's Laboratory

Penhoet: I didn't go over there and do a sabbatical with Bill, although by then, '78, he was doing a lot of recombinant DNA work. I went to do it with Brian McCarthy.

Hughes: Why did you choose McCarthy?

Penhoet: Well, Brian was a real leader in the field in those days. He had a number of very interesting projects going on.

Hughes: What was he working on?

Penhoet: Well, Brian worked on a variety of different things. People were working on yeast in his lab. His wife was working on *Halobacterium*. That's one of the things I went over to play with in order to learn how to do recombinant DNA technology. Brian was interested in a lot of problems related to gene regulation at the time. His lab was very active in the recombinant DNA field. I knew Brian, because Brian was at the University of Washington, too. Bill had recruited Brian to come to San Francisco from Washington.

Hughes: Oh, I didn't know that.

Penhoet: Bad commute, but other than that, it was an easy relationship I had over there. So then I got to know more of the people at UCSF--Pablo [Valenzuela] and some of the other people, just because I was working there.

More on UCSF Culture

Penhoet: I also observed first hand the culture of the place, which was probably more integrated than we were in Berkeley. There was a lot of collaboration between labs, and there was this sense of energy that you got there that people mention over and over again, which wasn't as evident here.

Hughes: Was the collaboration mainly within the department, or was it interdepartmental?

Penhoet: It was both.

IV POSTDOCTORAL STUDENT AND ACTING ASSISTANT PROFESSOR, SAN DIEGO, 1969-1971

Entrepreneurial Spirit and Intellectual Climate

Penhoet: I only applied for one postdoctoral fellowship, because I was sure I was going to get it, so there was no point in wasting any time doing another [application]. Nobody would do that today. But it was just the way we were. We thought we had the world by the tail. In terms of influences on my own career, San Diego was another place with a tremendous entrepreneurial spirit when I got there. I arrived in San Diego in January of 1969. At that point in time, the campus was seven years old, I think. I believe it got started in '62. So they were in a big building phase, expansion, building new colleges, hiring lots of new faculty. The Salk Institute [for Biological Studies] had been built just before that. Scripps Clinic was in downtown La Jolla at the time. So I found myself in another very expansive environment, full of people who were enthusiastic about the future, doing new things, hiring lots of new people, and also an outstanding group of people. The biology department at San Diego had recruited thirty or so faculty, and they were all top quality.

Hughes: Were they molecularly oriented?

Penhoet: Most of them, yes. But Salk was also hiring, staffing up, or had staffed up just before that, and had some great people. There were already really good people at Scripps as well. So again, quite by dumb accident, because I went to San Diego to work with John Holland and not to be part of the UC San Diego entrepreneurial atmosphere, I found myself in another place where the sky was the limit.

San Diego was a fun experience for sure, and a heady experience in the sense that by then, of course, I was better educated than I was earlier and could appreciate a lot more of the deeper intellectual content of what was going on in the

place. Those were the days, (it's probably still happening to some degree), when they used to have conferences at Salk where big brains showed up. Francis Crick always spent a lot of time there, as did Jacob Bronowski. It was more of an intellectual climate, I guess, than what I had been used to at Washington, which was more a medical school climate.

My wife had gotten a degree in educational psychology from the University of Washington, and that's her second master's degree. She had one in secondary education from Stanford. She became the Muir College counselor at UC San Diego, so she was part of the staff growth of the campus. My wife and I were quite involved in the campus life there in San Diego. I was a postdoc but I was accepted as if I were a faculty member almost from the beginning. Eventually, I was appointed as an acting assistant professor [1970-1971] and functioned as if I had been on the faculty. I didn't know any better, so I just pretended I was. I just thought that's the way it worked. [laughter] I'm a group-builder. So people end up wanting me to join things because I'll help them do something, whatever it is. I'm a consensus-builder and I join discussion groups and I talk too much, but I'm a contributor in that sense.

Research on Transfer RNA and Cancer

Penhoet: It was another building project, UC San Diego. We moved to the new campus while I was there and set up brand-new laboratories. Also my work was going well in San Diego. I struggled for a while because I was trying to learn a new field, virology, and I worked in a project area which didn't turn out to be very fruitful at the time.

Hughes: What was that?

Penhoet: Oh, trying to understand why cancer cells, transfer RNAs, are different than normal cells. They are different, and so we did a lot of studies doing comparisons, but it never yielded any new significant information that helped us understand cancer. It probably would now, but that was twenty-five years ago. But eventually while I was there I got involved in replication of viruses and discovered an enzyme which is key in the replication of influenza virus. That formed the basis for my later work here at Berkeley on viral replication.

Meantime, Clifford Grobstein--the person who got me started in science--had moved down there and was head of the biology

department, and while I was there became dean of the medical school. There was a group of pretty good developmental biologists there at the time, and I was interested in development. I only studied viruses as a way to figure out what was going on in cells. They were tools for me. In fact, they were a primitive way of doing cloning, and that's why I studied them.

Hughes: Was that the only way that cloning could be done before the Cohen-Boyer method?

Penhoet: Yes, they were the first clones; that's exactly what viruses were, and that was the advantage.

V PROFESSOR, UC BERKELEY, 1971-PRESENT

Appointment

Penhoet: Then it came time for me to get a real job, and that was somewhat daunting. That was the first time in my career I was worried about what might happen.

Hughes: [laughs] Up until then, everything had just been handed to you.

Penhoet: Well, almost. I worked hard, but still, it just all opened up in front of me all the time, so I never had to worry about what was next. But at that point in time, there weren't all that many jobs available. Fortunately, this job⁵ became available, and I had the right characteristics for it. They wanted to get into the field of mammalian cell regulation, et cetera. By then, Bill had been at UCSF for two years; they knew what Bill was doing over there. They knew that Gordon Tomkins was going to UCSF, and Gordon had been on this campus in early years.

I probably was a good candidate for them, because I was a card-carrying biochemist. So I was a card-carrying, authenticated, competent biochemist who was moving into the field of mammalian regulation. They wanted somebody who was going to do that, and they were probably comfortable with me because they knew, worst case, at least I was a competent biochemist. So I got the job and moved to Berkeley.

I'm sure Bill wrote me a very strong letter and helped in the process. I have no idea to what degree, but he's always been very helpful to me in my career. I'm sure he supported my application. So with Bill's help and whatever I did on my own, I

⁵ Penhoet refers to his position on the biochemistry faculty at Berkeley; the deanship came later.

got the job and came. My lab was in that building right there [Barker Hall] for fifteen years.

Hughes: It certainly was coming home, wasn't it?

Penhoet: Yes, although I had never been on the Berkeley campus before [in an official capacity]. I had walked around the Berkeley campus, but never been here as a student or anything else. I was born in Peralta Hospital, which is two miles from here, and grew up near Mills College. So this place was an important part of my growing-up experience. We used to come here as teenagers to hang out on Telegraph Avenue, just like kids do now. We didn't look exactly like these kids.

So in a sense, yes, it was a homecoming, an incredibly lucky one. If you had a career goal to get a job in the university in your own hometown, a great university, the probability you could pull that off is so low, it's not even worth thinking about it. But again I was just in the right place at the right time. I've had a charmed life; there's no question about that. Things just happen for me, and that was another of them. So I came here.

The Department of Biochemistry

Hughes: Tell me what you found when you came. By then you'd experienced several different departments in different institutions.

Penhoet: Yes. Well, interestingly enough, I almost changed my mind and didn't come here, because this department was undergoing a sort of transition. The students were very unhappy here the year before [1970-1971]. One of them actually came down to work with me in San Diego because he couldn't stand Berkeley. They sent him down there; they were happy to get rid of him. We're talking 1971 now, so it was a different kind of person than we have around here these days. It was a very conservative department.

Hughes: Which meant what?

Penhoet: The students thought that the department wasn't moving quickly enough into the so-called modern age of molecular biology. This was a biochemistry department, remember, not a molecular biology department. There were no molecular biologists here in those days. There was a split between biochemistry and molecular biology. Molecular biology was in Stanley Hall. Biochemistry was in Barker Hall. The biochemistry was very traditional biochemistry: protein chemistry, carbohydrate chemistry, et

cetera. It was more like going back to Illinois in some ways, or even further back.

Hughes: Molecular biology was an outgrowth of Wendell Stanley and the Virus Lab? The molecular approach?

Penhoet: Yes. Stanley hired a lot of these people here in biochemistry. At one time, it was one department, biochemistry and molecular biology, and then they got into a big fight and it split into two groups, molecular biology and biochemistry. That's when biochemistry at Berkeley was started as a separate discipline.

Hughes: And the more conservative souls stuck with biochemistry?

Penhoet: Right.

Eukaryotic Molecular Biology

Hughes: Were you the only one in the biochemistry department who was interested in the new molecular biology and recombinant DNA technology?

Penhoet: Well, at that time, there was no recombinant DNA technology.

Hughes: Oh, of course, '71.

Penhoet: This was '71. But they had hired another assistant professor named Greg Milman who was here before I came, for a year. But most of the rest of the people did classical biochemistry, so Greg Milman and I were it in terms of moving into eukaryotic molecular biology.

Shortly after that, money became available to help build up competence around the country in eukaryotic molecular biology. You could get some facilities money. So we recruited another young faculty member named Stu [Stuart M.] Linn to our little enterprise, the mammalian cell enterprise. Stu worked on DNA repair, still does. So Stu joined Greg and me, and we applied for funds to get a tissue culture facility here and build that up.

Turned out that was a crucial thing we did, because later on we hired Bob [Robert T.] Tjian, and that was a key recruitment that took us off in the right direction. One of the reasons he chose to come to Berkeley was we had this tissue culture facility

all built and ready to go and he was welcome to use it. So it was good we built it when we did.

In those days, the biochemistry department was a staid but friendly place. One of the things that was wonderful about coming here, in spite of the faculty being very conservative, is that my colleagues on the faculty accepted me as a peer almost from the first day. At least, that's how I perceive it. You know, this is all through my eyes. It could be that they thought I was just a brash young brat coming in here and speaking to them. But anyway, they were very supportive and accepting.

Hughes: Who was chairman?

Penhoet: When I came, Dave Cole was the chairman, and then later, Dan Koshland was the chairman.⁶ I'm trying to remember who else was the chairman at that time. Maybe Jesse Rabinowitz. Anyway, it was a good home. My assistant professorship wasn't all covered with glory. I had better moments and worse. The first grant I applied for, I got turned down. That was probably the low point of my entire career, because until then I didn't think anything bad could happen to me. I was made of Teflon; it was all going to bounce off. But I ran into a review committee which didn't like what I wanted to do, and I got rejected. Fortunately, I managed to get money from other sources and funded my research. I was moving off in a new direction. I always had--I still have --a tendency to bite off more than I can chew, so I've worked in quite a few different areas.

Hughes: Did you feel rather isolated, except for the one and then two colleagues in your field?

Penhoet: No, I didn't feel isolated. In a sense, they were the only people working on these things. But as I say, I was accepted as a peer in the faculty, and I think it's one of the great strengths of all these places around here. There is a difference between a tenured faculty member and an untenured one, but I think that most assistant professors come here and feel like they're real citizens from day one. It's a tremendous strength of our system that young people are not suppressed because you're most creative when you're young. That's the time to let people flower and try things and make mistakes.

⁶ See the oral history in progress in this series with Daniel E. Koshland, Jr.

Hughes: And that really was the case with you? There wasn't any skepticism about the new direction in which your biochemistry was moving?

Penhoet: Certainly none articulated to me. And before long, it was clear that that was the way a lot of the field was going to go.⁷ Things started to happen one after another in that era.

Interacting with Molecular Biologists

Hughes: Were you interacting with the molecular biologists?

Penhoet: Not much.

Hughes: Why was that?

Penhoet: Well, for one thing, they were a long way away on the other side of the campus.

Hughes: You didn't go to their seminars?

Penhoet: Oh, yes, sure, I did, because there were people working on mammalian cells up there. Peter Duesberg was there, and Harry Rubin was there. Who else was working on mammalian cell stuff up there? They would be the two principal ones, I guess, Peter and Harry. Peter had been working on RNA tumor viruses at the time, as was Harry. Mina Bissell was in the Lawrence Berkeley Lab at the time. So there were other people on campus working in related areas.

Department Retreats at Asilomar

Penhoet: The department was an old-fashioned, staid department in some ways at the time. In a funny way, it provided me with an opportunity for leadership in the department, because one of the things that I could contribute to the place was enthusiasm for getting people to think about new things. I ended up spearheading the search committees to hire some new people in

⁷ See the oral history with Daniel Koshland and the oral history retrospective of Marian E. Koshland for discussion of their incorporation of recombinant DNA in their research programs.

more modern biochemistry, as it was defined in those days. Mike Chamberlin and I helped start the tradition of having meetings for the department at Asilomar, getting people to work together. So my contributions to the department were partly scientific, but a lot cultural.

Hughes: Did that Asilomar model come from your experience at Stanford?

Penhoet: No.

Hughes: Where did it come from?

Penhoet: Well, people have been having meetings at Asilomar for years.

Hughes: Department retreats also?

Penhoet: No, I think we did it first.

Hughes: When did Stanford biochemistry and UCSF biochemistry began to have retreats at Asilomar?⁸

Penhoet: I don't know the answer to that. But we started doing these probably in '74. But many people had gone there for all kinds of society meetings, so people knew Asilomar.

Hughes: Was it the pattern for departments in other parts of the country to go as a group to discuss scientific matters in a different setting?

Penhoet: No. Whether we did it before or after UCSF, I don't know. We didn't pattern it after UCSF, and probably they didn't pattern it after us either. We probably independently came up with it. But we really were working to try to get the department to be more coherent and to have more exchange of information, so that's why we decided to do it.

The Biomolecular Approach on Campus

Hughes: Mike Chamberlin was on the cutting edge of this new approach?

⁸ For the answer, see Rutter's oral history and: Paul Berg, *A Stanford Professor's Career in Biochemistry, Science Politics and the Biotechnology Industry*, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2000.

Penhoet: Yes. He's spent most of his career working on RNA polymerase.

Hughes: He came a little bit later than you did?

Penhoet: No, earlier. Mike got his degree with Paul Berg, and then he came to Berkeley in molecular biology. He had a falling out with his colleagues in molecular biology and moved to biochemistry after I came here.

Hughes: I'm trying to establish the basis of this new way of doing biochemistry.

##

Penhoet: There were people in zoology; Fred Wilt studied development, for example. There were people in genetics doing molecular genetics. All these [research lines] have converged now, so the lineages go back in a lot of different directions.

Hughes: The picture that I'm getting from you is nothing like the cohesion of the enterprise at UCSF.

Penhoet: Oh, no. Not at all.

Hughes: Molecularly oriented people were scattered around campus and maybe sometimes came together, but it was not on any regular functional basis.

Penhoet: That's correct.

The Stanford Influence at Berkeley

Penhoet: There was a big influence of Stanford on these programs. Mike Chamberlin got his degree at Stanford; Richard Calender got his degree at Stanford; Stu Linn, who started doing DNA repair on mammalian cells, got his Ph.D. at Stanford. I had a degree at Stanford. Dr. [Horace] Barker got his degree at Stanford. Fred Carpenter, who was a professor here, got his degree at Stanford. There was a huge amount of Stanford influence on the Berkeley campus, probably significantly more than in the reverse direction, I suspect. Arthur Kornberg learned to do biochemistry here, in the laboratory of Horace Barker.⁹

⁹ For Kornberg's account of how he learned biochemistry, see his oral history.

Tension at Berkeley between Biochemistry and Molecular Biology

Hughes: Barker was a biochemist, was he not? He wouldn't call himself a molecular biologist, would he?

Penhoet: No, he would not. Nobody in that building [Barker Hall], including me, called themselves a molecular biologist. I don't call myself a molecular biologist today. On this campus, molecular biology and biochemistry were two distinct and very different things. This is a cultural thing. Here we had this split, and it was a deep split. I mean, real animosity; people not talking to each other. If you were a molecular biologist, you were up the hill and you were part of molecular biology; and if you were a biochemist, you were part of this group in Barker Hall], and that's how we were divided.

Hughes: That wasn't true of other campuses?

Penhoet: No. To this day, I don't think there's a molecular biology department at UCSF, right? Bill's [former] department is biochemistry and biophysics.

Hughes: There's no department of molecular biology at UCSF.

Penhoet: But they all call themselves molecular biologists. There were plenty of rifts at UCSF after Bill went there, because Bill, in addition to the FTEs [full-time equivalent positions] he got, had to clean out a lot of existing faculty [classical biochemists], who still dislike him for kicking them out. He didn't literally; you can't kick out a tenured professor, but Bill managed to talk them out. He made room for himself.

But since then, all those people over there have worked as a community. I'm not aware of any of the same kind of tension that there was here. This was a real divorce. And Wendell Stanley recruited the biochemists and the molecular biologists; they were all in Wendell Stanley's group. At some point, they got angry at each other and [whoo]. That's why we have biochemists and we have molecular biologists on this campus [in separate departments].

VI EMERGENCE OF THE BIOTECHNOLOGY INDUSTRY

[Interview 2: September 30, 1998] ##

Awareness of the Potential of Biotechnology

Gene Cloning at UCSF

Hughes: Dr. Penhoet, would you tell about the foundation of Chiron?

Penhoet: I think I told you before that I had a sabbatical at UCSF in '78. While I was there, Howard Goodman one day put the locks on all his freezers, because Axel Ullrich and Pete Seeburg had left his lab to go to Genentech. Howard was concerned that they had taken clones with them that belonged to him.

Hughes: Which they had, right?

Penhoet: Yes. So that was a tumultuous time over there, with the locks on the freezers, et cetera, and with those two guys going down the street with the clones. So you couldn't be at UCSF in '78 without sensing all of this foment about what was happening in the field. So I got a sense of that whole set of activities while I was there. I think it was the same year perhaps that Bill and Howard cloned the rat insulin gene.

Hughes: That was '77.

Penhoet: Interestingly enough, Wally Gilbert, was on campus here [at Berkeley] the day they announced they had successfully done this. Wally was their principal competitor and was here giving what subsequently has become the Chiron lectures, then known as the Smith Kline & French lectures, which is a very prestigious lectureship on this campus. I think I had dinner with Wally and some other people the night that Howard and Bill made this announcement that they had done the cloning of insulin. That was

just a curious sidelight in history, that while they had been doing this, Wally was here in Berkeley.

Cetus Corporation

Penhoet: Genentech was already going. Cetus was already going, although Cetus was in '78 not fully engaged in the recombinant DNA business. Cetus got started for a different reason. Don Glaser and Ron Cape and--

Hughes: Peter Farley.

Penhoet: Thank you. --Peter Farley started Cetus, probably in '71, to pursue the same technologies that Don had developed for doing selection of unusual microorganisms, mutants or variants or whatever you want to call them, on a mass scale. In about '78, or similar time frame, Cetus got quite engaged in recombinant DNA.

Hughes: If they were up and going as a biologically oriented company, presumably with ties to the universities in the area, why didn't Cetus jump on it sooner?

Penhoet: Well, first of all, nobody in that group had the recombinant DNA skills. Second of all, it was a UC Berkeley group, not a UCSF group. You might ask the same question of why the pharmaceutical companies didn't get involved, and it's partly because it was a little hard to be totally clairvoyant about what the future of recombinant DNA was going to be at the time. I don't know the specific reasons, but Cetus didn't wait too long. They hired a core of people to start their recombinant DNA activities.

David Gelfand was a key person in getting Cetus into the recombinant DNA business, and in fact, getting Cetus started in Emeryville. At the time, Cetus was in Berkeley, but Berkeley had passed some legislation which made it prohibitive to do industrial recombinant DNA research in the city. So Cetus actually started its recombinant DNA effort in Emeryville because it was forced out of Berkeley.

A former colleague of mine, Bud Colby, joined Cetus at about that time as part of the founding group for the recombinant DNA effort, and came to my lab on campus, because we wanted some reagents to conduct assays for interferon. Cetus's involvement in the interferon business was when Bud Colby showed up there. I don't know whether they'd done anything before or not. Bud was

an interferon expert. He was recruited to Cetus to work on interferon, and Bud came to my lab here, because we were old friends, to get some reagents to do interferon work.

In talking to Bud, I became aware of what Cetus was going to do. In the meantime, I was generally aware, because of the famous locks-on-the-freezer day, et cetera, of what was going on with Genentech and the controversy around the general issue of shared resources between UCSF and Genentech. So I was aware of what was going on in the biotechnology business, but I wasn't involved in any serious way at the time.

Amgen, Inc.

Search for a Research Director

Penhoet: Probably two years later, in 1980, I was approached one day by George Rathmann, who was then the CEO of Amgen, who asked if he could come and see me. He told me what he had in mind, so I agreed to meet with him to learn something about the industry. He actually came here to my office on campus.

Hughes: Had you known him before?

Penhoet: No.

Hughes: How had he found you?

Penhoet: Well, it subsequently came out that he found me because Bill Rutter recommended to him that he talk to me. Amgen was not founded by George Rathmann. George was recruited after Amgen was already started. Amgen was started by a group of venture capitalists. Probably the lead person was Bill Bowes. The first head of research was a guy named Winston Salzer, who is still a professor at UCLA, and the first CEO was probably Joe Rubinfeld, if I remember correctly. Then George Rathmann was recruited to Amgen by that original group.

Winston Salzer was research director of Amgen, but he was spending half time at Amgen and half time in his lab at UCLA. He wasn't willing to give up his job at UCLA and become full-time research director of Amgen. I think George felt, and rightfully so, that Amgen needed a full-time research director, so they began the search.

In the meantime, Amgen had assembled an outstanding scientific advisory board, actually put together by Winston Salzer. Maybe that was Winston's most important contribution to Amgen. And Bill Rutter was part of that advisory board. It was Norm Davidson from Caltech, John Carbon from UC Santa Barbara, and Bill Rutter. Who else was on that? I don't know, probably ten people. But anyway, it was a very good group.

George Rathmann, after he took over the company and sized up the situation, went to the scientific advisory board and asked their advice about whom he might approach as a research director. Bill Rutter gave him three names. One was mine, one was Pablo Valenzuela's, and the third was Dan Vapnik, who eventually did become the research director of Amgen.

So George showed up on my doorstep to discuss with me my interest in becoming the research director of Amgen. I spent some time on that issue. I was perfectly happy where I was here on campus. On the other hand, I'd had enough involvement in what was going on in the field to be intrigued--although I was not a central player in the whole recombinant DNA revolution. By then I was doing recombinant DNA work, and I knew the players, and I could see what was happening in that field.

Hughes: Had you before this approach from Rathmann considered moving into industry?

Penhoet: No. Not even vaguely. I just didn't have any interest in doing commercial stuff.

Hughes: It was lack of interest rather than any possible stigma attached to a professor moving into industry?

Penhoet: No, I wasn't worried about the stigma. I enjoyed what I was doing. I had made the decision some time earlier to go into academics, not into business, so I was perfectly happy with that decision.

On the other hand, by then the field was becoming intriguing. By the time George knocked on my door, Amgen had already raised \$20 million in venture financing. Genentech had already done a number of things. These friends of mine, Colby and Gelfand, had already gone to Cetus. So I thought, Well, it's at least worth talking to George to see what he has in mind. And George is a very persuasive guy.

I spent some time evaluating whether to leave this position here as a by-then-tenured associate professor and move to Thousand Oaks, California, which is where Amgen was, and become

research director of Amgen. Fairly early on, I decided I didn't want to do that. So I told George I didn't want to do it, and he moved on and continued the discussions with both Pablo and Dan. That was probably Pablo's first serious introduction to the field as well. I'm sure because of his position, Pablo was probably offered other opportunities before that, but I think Pablo got quite serious about doing this when George Rathmann got serious about trying to recruit Pablo. So Pablo was also talking to George.

Amgen North

Penhoet: Bill was on the scientific advisory board of Amgen and therefore got to know more and more about what was happening in the industry. At some point, Bill concluded that he couldn't continue to be competitive on several projects that he was pursuing in the University of California, particularly the hepatitis B project, because all of the people who worked for him, like Pablo, Graeme Bell, et cetera, were being offered compelling positions in the budding industry. So it really was Bill who decided to pursue some other alternatives. He was on the scientific advisory board of Amgen. So Bill was thinking about getting more involved, although at that stage he never anticipated leaving the university. Bill was going to become more involved somehow as an advisor. Ultimately, he became a principal in Chiron, but not as an employee.

After Bill realized that Pablo and I were both intrigued enough about what was going to happen in this business to have conversations with George, we actually developed a plan together, Bill and I and Pablo, about setting up a northern California branch of Amgen. One of the big barriers for both Pablo and me was neither of us wanted to live in Thousand Oaks, California. So there ensued a period of time when primarily Bill, because he was an insider at Amgen but also continuing discussions with me and Pablo, undertook to try to negotiate with Amgen the formation of a subsidiary of Amgen in San Francisco, Amgen North, whatever you want to call it. For a whole set of reasons, that didn't work out, so there was no Amgen North formed.

In the meantime, we had continued our conversations and became convinced that, well, if we faced the prospect of going to Amgen together, that Amgen's success or failure was going to be in large part dependent on how successful we were in the laboratory. At one point, Pablo and I thought about--at least discussed--the possibility we might both go there [Amgen North]

and take joint responsibility for their research programs. We continued to discuss this, and in the end, we decided, well, we have the scientific skills but we don't have George Rathmann and we don't have \$20 million. So we were lacking two important components.

George Rathmann

Hughes: What did George Rathmann offer?

Penhoet: Oh, he offered a good salary and stock options.

Hughes: I meant what did he provide that you and Pablo didn't have?

Penhoet: Well, George had much more business experience. He had spent his life in industry.

Hughes: As a scientist?

Penhoet: Well, no, as a manager. It had been a long time since George actually did any science with his own hands. But George managed science at 3M and at Abbott Laboratories. George was always a broadly conceptual person. He had much more business experience. We probably gave him credit for having more business experience than he actually had at the time, [laughs] which is another matter. But he did come from Abbott; he didn't come from UC. And George is a broad-gauged person, a talented man. And he had proven he could raise \$20 million, because he had done it by then. Bill helped raise the money; Bill went out and gave some talks on Amgen's behalf. Amgen didn't raise all the \$20 million right the first day, but they raised it over a one-year period or something like that. So some of it was undoubtedly already there when George got there, but I think they continued to raise the money and got to \$20 million after George was on board.

The things that made it attractive to go to Amgen were they had the \$20 million; they had in George an experienced manager running the company. But the downsides for us were, Amgen was in the wrong place, and second of all, it was a very unfocused organization. Amgen was then intending to work in lots of different fields. It was a little bit like Cetus. Amgen's business plan at the time involved energy, dye stuffs, plants, diagnostics, therapeutics, and we thought that this was much too broad an agenda to successfully compete.

Hughes: Was that broad agenda somewhat because of the commitments Cetus had made in terms of the investment community?

Penhoet: Yes, I think they got \$5 million from Tosco Oil Company, for example. So Tosco expected them to work on some energy-production project, bioconversions or things like that. So we decided not to do that.

Increasing Interest in Commercial Biotechnology

Early Biotechnology Patents

Penhoet: But in the meantime, we continued to say to each other: we don't have to do Amgen. Other companies were being formed, and there was a lot of activity in the field at that time. Cetus was ramping up its recombinant DNA programs. Genentech was continuing to hire first-rate people. Biogen by then was better known. Then the Chakrabarty patent was issued somewhere along in that time frame.

Hughes: 1980.

Penhoet: Yes. So that stimulated further interest on the part of the financial community in backing biotech ventures.

Hughes: What about the Cohen-Boyer recombinant DNA cloning patents? Were they having any influence on this thinking?

Penhoet: Well, they were issued later. But not much later.

Hughes: The first one issued in December 1980. Which of course is after some of the biotech companies had been founded. Did these patents cause a hesitation?

Penhoet: No, because all the early patents were viewed as positive, because if you couldn't protect this intellectual property, then people were not going to invest in the field. So it was the fact that patents would issue, even if they were in your way, that gave people confidence that the field would be able to create value. And I don't think anybody believed that UC and Stanford would pursue a restrictive licensing policy for the Cohen-Boyer patents. They were too fundamental, in a sense. And they never discussed that.

The patents issuing were a stimulus to the formation of the [biotechnology] field, because people said, "Oh, yes, I see patents will issue in this field; you can patent life forms; you can patent genes. Therefore, if these guys discover new genes, they're going to be able to get patent protections for them." So the patents issuing really were a stimulus for the industry, a significant stimulus.

Science magazine had articles practically every week on what was going on in the field. It was already getting warmed up by the time we got involved, although the time we were having these conversations was probably the most fertile single period in the formation of new companies, the 1980-81 time frame. It was during that time the Chakrabarty patent did issue, and the Cohen-Boyer patent was coming. By then, Genentech had probably expressed insulin and talked about it.

Initial Public Offerings

Hughes: Also Genentech had an initial public offering with a huge escalation of stock value. Remember that?

Penhoet: Yes. That was in the 1980, '81 time frame as well [October 1980]. And Cetus had the second largest public offering, IPO, in history.

Hughes: In any field?

Penhoet: Yes. Before that, Ford Motor Company was the largest. Cetus raised \$100-some odd million. So by then, the temperature of the whole set of discussions was markedly increased, and lots of people we knew were getting involved, which is part of the dynamic, there's no question about that. A critical mass of thinking people were talking about this kind of thing.

Chiron Corporation

Decision to Found a Company

Penhoet: Bill and I and Pablo had significant discussions around this whole area: should we do it? And if so, how should we do it? Et cetera. We continued to evolve a plan to a point where we said,

"Well, if we're going to do this, we don't have George and we don't have \$19 million, but we can get some money, and we have reasonable enough management skills, having managed big labs and people." I at least had had some business experience.

Hughes: How did you know you could get the money?

Penhoet: Well, we didn't know we would get the money. On the other hand, in retrospect, it's hard to imagine that we wouldn't have gotten the money [considering] Bill's reputation as one of the three or four leading people in the entire field. I by then was certainly a credible individual, based on my work at Berkeley. Pablo had contributed a lot to recombinant DNA. Venture capitalists bet on people. If we weren't going to get funded, who was? So we convinced ourselves that we would get money because we had projects.

The hepatitis B project that Bill and Pablo had been working on was by then moving along very well. We had a number of other things. We knew a lot about infectious diseases and about polypeptide growth factors, and those were two areas where all three of us had worked in the past and had relevant skills. What we lacked was a business person, but I think that all of us had enough business savvy, if you will, to convince somebody that we could make a go of this.

Hughes: Do you remember being questioned on that point?

Penhoet: Oh, sure, extensively.

We wrote a business plan, and then we began to discuss it with a few people.¹⁰ We also had a problem in the sense that even though we had decided to start the company, George Rathmann was still busy recruiting people from UCSF. My impression is that Pablo had virtually accepted the job at Amgen and was in the process of recruiting the very same people in Bill's lab and around us that we eventually wanted to recruit to Chiron. So we had to convince all those sort of next-level people that they should take the risk and come with us, even though we didn't have any money, and we didn't have any George Rathmann.

¹⁰ The first business plan for what was later named Chiron and a few other documents related to the company's early history are online at: <http://www.lib.berkeley.edu/BANC/Biotech/exhibit>.

Pablo Valenzuela

- Hughes: Do you think Pablo's eventual decision to come with Chiron was because of his personal relationship with Dr. Rutter, or was it to do with the potential for this new company?
- Penhoet: I think it was probably two things. I think it was primarily his loyalty to Bill and his longterm relationship with Bill. And second of all, I think Pablo got a bigger slice of the equity in Chiron than he would have gotten in Amgen. As it turns out, that smaller slice of Amgen would today be worth more than the bigger slice of Chiron.
- Hughes: [laughter] But who was to know?
- Penhoet: There was no way to know that at the time. I believe Pablo was also concerned about the lack of focus at Amgen. It's ironic, because Chiron is today seen as the company that's not focused and Amgen is focused, but in the beginning it was the other way around.

First Business Plan

- Hughes: What was in Chiron's first business plan?
- Penhoet: We wrote what we thought was a business plan, but it was in fact a product plan. First of all, we assembled a description of the skills we had as a group of people, and second of all, the specific projects that we were going to take to create value in the field of biotechnology. We articulated a business plan which anticipated some forward integration as the company grew, at least into manufacturing.

The product plan area basically had three areas. One was vaccines, one was diagnostics, and the third was polypeptide hormones: insulin, EGF [epidermal growth factor], IGF [insulin-like growth factor], nerve growth factor--a number of growth factors. So it was basically growth factors and infectious disease, with an emphasis on hepatitis because the hepatitis B project was the first project we were going to actually work on. So we attempted to get some estimate of the size of the markets that these products would face.

Merck and Lilly

Penhoet: We stressed the fact that we would have a relationship with Merck up front. It was very helpful. The Merck relationship has not been tremendously profitable for Chiron, but it was a validation of the quality of our group for sure because Merck even then was considered the most sophisticated of the pharmaceutical companies.

Hughes: The Rutter lab also had a relationship with Eli Lilly.

Penhoet: Yes.

Hughes: Did that count as well?

Penhoet: Well, probably, although we never consummated a deal with Eli Lilly at Chiron. We attempted to do a deal with Eli Lilly to pursue IGF, but Eli Lilly in the end decided not to pursue that with us.

Charlie Crocker

Penhoet: And then you asked about raising money. Part of what made it relatively easy is that there were so many venture capitalists around here. In the very beginning, we enlisted the help of one minor venture capitalist at that time, a man named Charlie Crocker. Charlie is part of the banking family. There is no Crocker Bank any more. I guess it was probably Charlie's great-grandfather who was part of the "big four"--Stanford, Crocker, Huntington, and Hopkins. Charlie came from a wealthy background, and Charlie was an individual investor-type venture capitalist. Bill knew Charlie because Bill and Mickey Urdea, who is still at Chiron, had started a little company which they had sold to a company backed by Crocker.

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Penhoet: Maybe it really was a probes business rather than a synthetic DNA business, to try to do probes for diagnostic things; I'm not sure. The company was called Biopolymers, and Mickey Urdea and Jim Merriweather were working there. Bill owned part of it. This company was set up a few years before Chiron. It must have had a diagnostic intent.

Before we started Chiron, Bill and Mickey, and C. K. Chang I think was involved in this, sold it to Hana Biologics, which was a company backed by Charlie Crocker, and by a person named David Rammler, who was a former research person at Syntex Laboratories. (David got his Ph.D. here at Berkeley in our department.) Bill knew Charlie, and I didn't know Charlie well, but my wife grew up with his sister, so she knew Charlie a little bit. So we had some connections to Charlie Crocker.

Charlie played the role of wealthy backer for us. He made a presentation to all these scientists, Graeme Bell and others, who were worried about our ability to finance this project and who were about to go to Amgen. So Charlie played an important role in convincing them not to worry, that he would help raise the money for this new company, and it would be fine. Charlie was put in front of these guys as a representative of the financial community.

As a result of that, and as a result of Hana Biologics agreeing to provide us with laboratory space, when we founded the company, we actually created a fair amount of stock and provided it to Hana Biologics. It was going to go to Charlie Crocker, but then later the Hana people said, "Well, you wouldn't have met these people without Hana, et cetera." So it didn't go to Charlie individually; it went to Hana Biologics. Hana put in a small amount of money up front in Chiron, so Hana had--I'm trying to remember how many shares. It was a lot of stock, looking back on it.

Approaching Venture Capitalists

Penhoet: So we actually got a little seed money from Hana Biologics and from Bill and myself. I think we put in \$100,000--\$50,000 apiece--and Hana Biologics put in \$100,000, if I remember correctly. Something like that. Then we began the process of talking to venture capitalists. We went to Jean Deleage first because he actually had approached Bill at some point in the recent past. Jean Deleage had told Bill that if he, Bill, ever wanted to start a biotech company, that he, Jean Deleage, would be interested to back him. So Bill remembered this and called Jean Deleage and set up an appointment. Then we started a round of discussions with Burr, Egan, and Deleage. In those discussions, there were lots of questions about our management capabilities, how we would do this, how committed we were, and all the rest of these things.

We also had the idea right up at front, and this was Bill's idea, to earmark some of our stock, Bill's and mine, to be given back to the university, to recognize the general contribution the universities had made to the founding of Chiron. We hadn't made specific deals on the technology transfer, et cetera, but sort of recognized the parentage, if you will, of this whole thing. Eventually, we donated some stock, Bill to UCSF and I to Berkeley. \

Hughes: Was that unique?

Penhoet: Yes. I don't think anybody else has done it before or since, as a matter of fact.

We sent around a business plan and spoke with several different venture capital groups. One was Burr, Egan and Deleage, one was NEA (New Enterprise Associates), a third was one on the Peninsula, Sutter Hill Ventures. Those were probably the three key ones we talked to.

The people at Sutter Hill became quite intrigued because at the same time they had a proposal from another group in Boston, which eventually became Integrated Genetics. The people at Sutter Hill Ventures thought, Well, wait a minute. This is an interesting marriage. The guys in Boston have a strong management team. The CEO, Bob Carpenter, came from Baxter Laboratories; he was a highly regarded businessman. He had strong business skills and weak science. We had strong science and ostensibly weak business skills. Certainly in comparison to Bob at the time, that's what you would have concluded.

David Anderson at Sutter Hill Ventures decided that an early merger of Chiron and Integrated Genetics would be a good idea. We had a long series of conversations with him about merging right away with Integrated Genetics, forming one company that had strong management and strong science. We decided not to pursue that. It was too cumbersome: one group on the East Coast, one on the West Coast. We were too naive to recognize the value of the business skills at Integrated Genetics. We thought we could probably do this just as well. In the end, we decided to go it alone.

The whole process of venture capital raising was pretty rapid. We wrote the business plan on the Easter weekend of 1981 --the product plan, as we now know it was. And we started the company on the first of June, so only two months intervened in between. The whole thing didn't take very long. But we spent a lot of time deep in conversation with people about how this would work or wouldn't work or whatever.

Hughes: What should you have included but didn't to make it a business plan?

Penhoet: Well, we didn't have good projections of financials. We didn't have a well-articulated commercialization strategy. We knew what the products were--which is the heart of it. In our field, if you have good products, you will somehow make money. But we didn't have the other commercial parts fleshed out. But it was good enough for Deleage.

Risks

Hughes: And none of this worried you three?

Penhoet: Yes, sure it did. We were worried about every aspect of it. Of course it was a risky venture, so we were worried about all of it. On the other hand, if you're successful at what you do-- At the time, we probably didn't have the same perspective as I do now. But in Bill's case, what was he worried about? He wasn't leaving his job at UCSF, and he's a hard worker, so spending even more time working was not a problem for him. Pablo didn't have a regular faculty position at UCSF and was going back and forth to Chile. So of the three of us, I was taking the biggest risk because I was contemplating leaving a tenured faculty position in a great university, although when we were doing the business plan, I hadn't committed yet to resigning my position. I was committed to taking a year or so to try it, either as a partial sabbatical or a part-time position, depending on the way things developed.

Hughes: Did you resign your tenured position?

Penhoet: Eventually [1983], but not right away. In '81 when we started the business, I went half-time at Berkeley. I wasn't sure they'd grant me that, by the way. That was a risk right there.

Genentech as a Model and Competitor

Hughes: Was Genentech figuring in your thinking in any way?

Penhoet: Sure.

Hughes: It was the first biotech startup. It was in the Bay Area. You knew a lot of the scientists that were involved. Would you go so far as to say that it was a model?

Penhoet: Sure. There's no question it was a model for many of us. First of all, Genentech had already successfully traversed a lot of the ground that we would eventually cross ourselves. They had filed a lot of patent applications, so they had defined, in a sense, the intellectual property landscape. They had raised a lot of money, so they proved it could be done. They had recruited outstanding scientists. Ten years later, six years later, something like that, the reason this campus reinvested in biology [the reorganization of biology at Berkeley in the 1980s] was because Genentech was publishing more papers than the whole UC Berkeley campus in the biological sciences.¹¹ So there was no question it had a big impact.

Genentech had started earlier than we did, but the competition between us and Genentech was fierce in those days, because Genentech had been successful with some things, but some of them were directly competitive with UCSF, insulin being one of those. Growth hormone was the reason that Howard [Goodman] locked the freezers that day.

Our product line had a lot of overlap at the time with what Genentech was trying to do. So this was a horse race. I think that was very important in itself, and it probably made both companies more successful. It's a little bit like Sosa and McGuire: there's nothing like a good competitor breathing down your neck. And in those days, it was quite personal, one on one. Chiron and Genentech were small companies; everybody knew everybody else. We sort of knew on a daily basis practically where Genentech was on the projects. We were both working feverishly on hepatitis B vaccine, for example.

Hughes: What was the source of your information?

Penhoet: Oh, it was just-- People talk and brag to one another. Of course, it's not good business practice.

Hughes: Was there so much to do with this new technology that it didn't make much difference that Genentech had a jump on the field?

¹¹ For the history of the reorganization of biology at UC Berkeley see oral histories in progress with Daniel E. Koshland, Jr., Roderic Park, and Louise Taylor.

Penhoet: Oh, no, it made a big difference. We were playing catch-up with them for a long time.

Hughes: And so was everybody else?

Penhoet: Well, Biogen had contributed a fair amount in those early days. From a technical point of view, Biogen and Genentech were the leaders. They were sort of in a class by themselves. Then there were the second-generation companies with good science. The best of those were Genetics Institute, Chiron. Amgen wasn't considered to be a scientific powerhouse at the time, but Dan Vapnik was a good guy, their research director. Who else was scientifically noteworthy? Not many. There were only eight to ten first-rate science-based biotech companies.

Hughes: Well, CalBio [California Biotechnology, Inc.],¹² but that's a different field.

Penhoet: Oh, yes, John Baxter had started CalBio. That's true.

Choosing Development Areas

Hughes: In choosing research or product areas, were you primarily thinking of your experience with projects started in university labs? Rather than deciding, Well, Genentech has taken insulin and growth hormone, so we'll develop vaccines.

Penhoet: It's a combination of both. We had purposely avoided interferons, because by 1981 they were already being divided up among Biogen, Genentech, Cetus--everybody in the world was working on interferon. And we didn't have anything particularly novel to bring to that competition. So that was one product area we deliberately avoided.

But at the time, there were a finite number of things that you could contemplate with the technology. That's one of the reasons why people in the pharmaceutical industry thought [recombinant DNA] was going to be a flash in the pan: you'll do the twenty proteins on the list, and when you've exhausted the list, it's over.

¹² The company is currently called Scios.

Hughes: I thought it was the opposite case, that there were so many potential projects out there that it was a problem of choosing among them.

Penhoet: No, not in 1981. At the time we started, there was a list of known proteins. "If you can make these proteins, they will probably be useful as therapeutics." The worst problem we had in the early days in the industry was everybody was working on the same thing. If you looked at Amgen's list, it was the same as Chiron's list, same as Genentech's list.

Hughes: Why was that list short?

Penhoet: Well, because people weren't aware of many whole classes of molecules.

Hughes: So it was a basic science problem.

Penhoet: Yes. [telephone interruption]

In one sense, that first decade of biotechnology was more a horse race than anything else. It was like an Easter egg hunt or something. It was a very finite list, and it was a competition of who could go the fastest and get there first.

Work Ethic, Information Leaks, and Competitiveness

Hughes: How does a company get people going, particularly on a sustained basis?

Penhoet: Well, first of all, I think we talked before about the strong work ethic at UCSF, and how this permeated all the Bay Area companies. I think that gave the San Francisco companies an edge, although successful people in science everywhere work hard. But maybe people at UCSF took it to an extreme.

I think it's hard to know exactly who the spark plug was in individual companies. Certainly at Genentech, Dave Goeddel was known as--well, I don't mean to use a derogatory word--a fanatic worker. David is capable of a sustained level of effort over a very long period of time and is extraordinarily productive. Both Axel [Ullrich] and Peter Seeburg were very intense people who also work really hard. So I think those three guys probably defined the work ethic at Genentech.

And at Chiron, probably more than any other person, Pablo. Pablo is unusual in the sense that he doesn't have any energy barrier. Some of us think about things for a while before we get started doing things. You could have a discussion with Pablo about a new project, and an hour later he's already got it going in the laboratory. He's really unusual in that regard. So Pablo has a bias for action which is very important. I suspect the people around here understood the nature of this game.

The downside of people talking to each other across these companies, which they shouldn't have been doing, was that they were probably sharing proprietary information in some sense of the word--maybe not intellectual property in the legal sense of the word. But they might have been better off in some worlds keeping their mouth shut. But the fact that they were sharing information certainly fanned the flames of competition.

Academic and Industry Cultures

Hughes: What about the change in culture from university to industry?

Penhoet: Well, because it was a horse race, people knew, well, the company will be successful if I win the race. I'm not sure in the early days that the companies were forced to confront this difference in culture. I didn't see much difference.

Hughes: Is there one now?

Penhoet: Increasingly so, because the companies are larger. When Chiron went public in 1983, two years after it was born, we only had forty people. Forty people is a big university lab, but it's not unheard of in a university lab environment.

Hughes: You're meaning that it was easy to instill the academic culture at Chiron?

Penhoet: Yes.

Intellectual Property

Penhoet: There was an extremely important assumption that was underlying the whole industry formation at the time. That assumption was that intellectual property was going to be created and sustained.

Because what did transfer to business from the university environment was publication. The people in the companies published their work every bit as regularly and as aggressively as their academic colleagues. In that sense, they were in one pool of publications with their academic colleagues, and that was true of the industry practically from the first day. So that tradition of publishing research results only could have existed if people had a belief that intellectual property was going to be protected. Otherwise you couldn't publish your results.

That's still an underlying factor in the business today. It's in fact invaded all the other health care companies, so everybody publishes now, whereas people were very reluctant to publish in the past in some corporate environments. But now they can't keep good scientists unless they let them publish.

Hughes: Are you saying that the system moved from trade secrets to patents?

Penhoet: Well, drug companies always patented their products, the individual chemicals and stuff.

Hughes: But my understanding is that, at least in the early days, pharmaceutical companies relied heavily on trade secrecy.

Penhoet: Yes, they did.

Hughes: But you're saying that wouldn't work in the biotech industry?

Penhoet: Well, it didn't work. One of the reasons why good scientists were willing to go to biotech companies and not willing to go to a pharmaceutical company was because they could have their cake and eat it too. To put it in plain terms, they wanted to be rich and famous. So they could have it both ways, but you could only have it both ways if you believed that patents were going to be useful. Because otherwise, you couldn't give away all your secrets, which you do when you publish. You would have to forego being famous.

Hughes: Yet the story is that a true understanding of patents was not pervasive in the biology community when all this began to take off, say in the seventies. I know from the history of the Cohen-Boyer patenting process that it took a lot of educating before the scientists involved understood what patenting really meant.

Penhoet: They didn't have to be involved. They only had to know one thing. Say you're a scientist, Sally. I say to you, "Sally, don't worry. You can come to Chiron and when you get important results, you can publish them." That's the only level they had

to understand. I, as head of the company, had to know about the patent system. But individual scientists didn't have to concern themselves with the intricacies of the patenting system. They had to know the bottom line: What does it mean for me? Bottom line is you can publish your work. It's all they needed. Right, I'm on board.

Take Graeme Bell, for example. Graeme is now a professor in Chicago who was one of the Chiron gang in the beginning. If you had said to Graeme, "Graeme, we're going to start this company, but we can't publish our results," Graeme wouldn't have thought about it for ten seconds; he never would have joined us. So the assumption in the industry was that a scientist could publish, and it wasn't that scientists needed to understand patenting. Investors needed to understand it, and management needed to understand it, but the bottom line for scientists was simple: You can publish.

Chiron's Initial Assets

- Hughes: What was Chiron's patent position when it was first taking off? What did it have going for it?
- Penhoet: Well, really nothing. Intellectual property is something you create out of whole cloth.
- Hughes: I know Dr. Rutter was an inventor on at least two patents, through the university.
- Penhoet: They weren't assigned to Chiron. We had no access to any of those. So we had to create our own intellectual property. We didn't bring any with us as a dowry from some place.
- Hughes: A venture capitalist didn't expect a new company to hold patents?
- Penhoet: Right. I mean, it was nice to have them. We brought [from UCSF] a contract from Merck on hepatitis B, and we brought a broad understanding about how the rewards would be split among several entities at the time.
- Hughes: And you brought three people [Chiron co-founders] experienced in the field that you wished to explore. What else did Chiron have to offer?
- Penhoet: Well, some reasonable product ideas. We didn't have a sophisticated business plan, but we had a reasonable idea what we

could do with this technology and where it could make an impact. So we had a point of view about vaccines, partly because the hepatitis B work was moving along well by then. We knew a lot about a class of substances called growth factors that are related to insulin and other polypeptide hormones, and we thought we knew what these could be used for.

We knew the opportunity available in the field of what was then called non-A, non-B hepatitis. That one was not on everybody's list. We had a limited universe of competitors in biotechnology for what eventually became hepatitis C. Most people in '81 didn't recognize hepatitis C as the pervasive problem it was, and really didn't know how to go about solving the problem even if they did.

Hughes: Was the hepatitis C project an outgrowth of the hepatitis B?

Penhoet: Yes, to some degree. At least Bill knew the hepatitis field as a result. [telephone interruption] Hepatitis C wasn't unique to us; there were other people working on it. It wasn't part of the universal list. Hepatitis B vaccine was on practically everybody's list. Things like factor VIII for blood clotting were on almost every list because they were obvious things to do.

Chiron's Early Focus on Vaccines

Hughes: Was it always anticipated that vaccine development would be a special interest of Chiron?

Penhoet: Yes.

Hughes: That was not a common orientation of early biotechs, was it?

Penhoet: No, it wasn't. But as I said, hepatitis B vaccine was. So you had to assume that people might have had ideas of other vaccines in the back of their mind. If they could do hepatitis B, it's not a huge conceptual leap to think that you would do other vaccines. But we had a focus on vaccines which was probably unusual at the time.

Hughes: Did investors like that focus?

Penhoet: Oh, they varied in their response to that. Some did and some didn't. I think they appreciated the fact that it was a field with broad potential. Most of the biotech investors were fairly naive about the pharmaceutical business; it wasn't their

background. So if you had a sensible argument and a way to make money in the field, they were more interested than the pharmaceutical companies were. We had a hard time getting any pharmaceutical companies interested in supporting any vaccine work because they were not convinced it was a good business.

Hughes: Yes, there had been a history of liability problems.

Penhoet: Yes. In general, we had some skeptics about the vaccine business, but I think people saw it as a useful field. It was the one area that clearly distinguished us from our competitors.

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Hughes: Did potential investors' lack of biological knowledge make it more difficult for you to get Chiron's mission across?

Penhoet: Oh, probably. It's always hard to sell somebody on something which is totally conceptual to them.

The First Round of Financing

Penhoet: I just told you it was relatively easy for us to raise the first round of financing to get the company started in 1981. I have two reasons for that: because of our reputations, particularly Bill's reputation in the field, and second of all, because we weren't looking for a lot of money. We took an approach to the subject which assumed that we could finance ourselves as we went along, because, frankly, we didn't want to suffer the same kind of dilution that Amgen had already gone through. We had that experience in front of us.

Hughes: Wasn't there possibly a third factor, too, namely the national economic context? 1981 was the peak year for the foundation of biotech companies.

Penhoet: Well, it wasn't because there was a great stock market. It was because the Chakrabarty patents issued; it was because Genentech and Cetus went public. Ultimately, any of the venture capitalists we talked to would have invested in Chiron. We didn't have any trouble getting money. We could have taken money from one, two, three, four--however many we had contacted. They all said yes. We decided just to go with Deleage because we talked to him first and it was the simplest.

But one year later, it was extremely difficult to raise any money for biotechnology. So we were scraping; we were really seriously questioning whether we'd be able to pull it off or not. That's the fickle nature of financial markets. And at the time, lack of sophistication in many of the people we talked to was an issue. During our fund raising efforts, we talked to one of the founders of Federal Express in his office in New York. He fell asleep in the middle of our presentation. We had other people liken what we were doing to being wildcatters drilling oil wells. Well, maybe that's not a bad analogy, who knows? So it was very volatile in those days. Genentech, as you may remember, went public and had a spectacular [stock] run up. But then their stock plummeted the next year. Lack of sophistication leads to a high degree of overreaction. When things go badly, people get more worried than they should. Conversely, when things go well, they get overly optimistic.

Research Timelines and Over-Optimism

- Hughes: Did you also try to get across the longterm nature of R&D, that it takes sustained financial and scientific investment in order to arrive at a pharmaceutical product?
- Penhoet: Yes. Although we were naive ourselves about how long it would take at the time. We were much more ambitious about timelines in those days than it turned out was realistic. I think most people in the field were. It would have been hard for us to imagine that it would take twenty years to develop betaseron for multiple sclerosis. So we probably were overly optimistic ourselves about definite time frames. That's the nature of entrepreneurs. People who are pessimists by nature will never go do this. So it's almost a sine qua non in the field that you're going to have it populated by people who are overly optimistic about the future, because they're the only people who would take the risk. And they're all self-selected.

Bay Area Research Universities

Integration of Basic Science and the Clinic

- Hughes: The three research universities in this area are UCSF, Stanford, and UCB. As we've also said many a time, UCSF was first off the mark.
- Penhoet: Well, first off the mark in application of this technology to medical problems. The people at Stanford would probably dispute the notion that UCSF was the first off the mark scientifically.
- Hughes: Oh, yes. I'm talking in terms of the industry.
- Penhoet: Right. UCSF was uniquely able to get the clinicians involved with the basic scientists, and together they figured out that they could use this new technology to make dwarfs grow or solve insulin problems or make a vaccine for hepatitis B. People like John Baxter played a significant role in this. John was both a competent physician and a competent molecular biologist. John understood endocrinology on one side, and he was working with Howard Goodman and Bill and these people armed with the molecular biology approach on the other side. John is a walking example, if you will, of the integration of basic science and medicine. It's probably that that UCSF did best.
- Hughes: Arthur Kornberg is an M.D., but he is an M.D. functioning as a basic scientist, isn't he?
- Penhoet: Oh, yes, in a totally different way than John. Arthur has an M.D. degree, but that's an accident of history. There's a difference between an M.D. and a physician. John ran the endocrinology clinical division at UCSF. He was, maybe still is --I don't know exactly what John's job is now. I know he's not head of endocrinology any more. John saw patients in those days, I'm sure. Arthur wouldn't know a patient from the man in the moon.
- Hughes: Stanley Cohen has a joint appointment in genetics and in medicine and has been doing clinical work all along. He didn't found companies, but he was a scientific advisor to Cetus.
- Penhoet: That's true. But part of the problem at Stanford was its balkanization.
- Hughes: Yes, Kornberg and Cohen were in a medical school, as the people at UCSF were, but what a different outcome!

Penhoet: But not integrated in the same way. I don't know the Stanford situation all that well, so you'd have to ask somebody at Stanford.

What was unique about UCSF, and still is to this day, is that they're trying to make sure whatever they do, they preserve the integral quality of the place where medicine and basic science are to some degree intertwined. The Stanford Medical School practice part was in San Francisco. When it moved to Palo Alto [1958-59], the molecular biologists came to the medical school, the molecular biologists being Arthur Kornberg, Paul Berg, and Josh Lederberg. They all came basically at the same time: '57, '58, somewhere along in there. They moved there en masse; they landed there. But the people who practiced medicine at Stanford were not colleagues in any sense, I'm sure, because they had a totally different background.

Hughes: Also the Stanford department of biochemistry had a policy opposed to joint appointments.¹³ That wouldn't probably have happened at UCSF, right?

Penhoet: No, it didn't happen at UCSF. Because see, UCSF had very little before 1970. UCSF's strength in both medicine and basic science grew up together. They became prominent together in the seventies; they grew up together in the school of medicine. They were put together in the sixties by Holly [Lloyd Hollingsworth] Smith and others. Whereas at Stanford, they didn't grow up together. The biochemistry department came as an entity. It landed there--

Hughes: Preformed.

Penhoet: Yes. Totally preformed. And it's been one of the great departments in the world ever since. But it hasn't been part of the Stanford Medical School [in terms of collaboration with the clinical faculty]. It could have been anywhere. They could have decided, We're going into biology instead. It wouldn't have made a lot of difference in the way it progressed. It didn't, because Arthur is an M.D. Paul was not.

Hughes: Dr. Rutter said in the oral history that he was reluctant to give joint appointments in the early days, because he was afraid of losing power, of losing control.¹⁴ The impression I got was that

¹³ See the oral history in this series with Arthur Kornberg.

¹⁴ See the oral history with William J. Rutter.

he wanted to have the biochemistry department on a secure footing before he branched out.

Penhoet: I'm not sure that joint appointments are the essence of what we're talking about. A joint appointment is a formality. You don't have to have a joint appointment to get people to work together. That's a different issue.

Hughes: Well, why do departments have joint appointments?

Penhoet: I don't know. It's more window-dressing than anything else. There's no reason to. It formalizes a cross-disciplinary person. Maybe it says more about the person. The joint appointment to me is a concept, and that's where UCSF was. Whether they had any formal joint appointments or not, they had a community of interest. I think that's what was different than Stanford.

Recombinant DNA and Biotechnology

Hughes: Berkeley was the last of the three universities to enter the recombinant DNA/biotech field.

Penhoet: Yes. Well, first of all, Berkeley had no medical school, so when it came to applying this technology to medical problems, there were probably only a handful of us on campus whose work could have impacted medicine in those days. Those were people working in infectious disease. Peter Duesberg was one of those. He was slow to adopt recombinant DNA technology to his program in retroviruses.

Hughes: Do you know why?

Penhoet: Well, he was good at doing what he did.

There was a cancer research lab here in those days, but those people didn't do recombinant DNA work at all. So really, Berkeley was a place where fundamental biochemistry was much better developed. That's much more important now. But in those days, it was more people closer to the medical problem who adopted recombinant DNA.

So I think it was partly that people here didn't have the same interests. Because people here were already successful doing what they were doing, at first there was no big reason to jump into a new area. Also, Berkeley in that era didn't have a huge number of FTEs [full-time faculty equivalent positions] to

hand out, so it was hard to build by hiring new people in any significant numbers, like Bill was doing at UCSF. But Berkeley always had the underlying science very well represented. Eventually, of course, recombinant DNA became such a powerful tool that people here had to use the tools.¹⁵

Views on Faculty Ties with Industry

Hughes: What was the sentiment about commercial activities on the Berkeley campus?

Penhoet: Certainly there always was a negative view about commercial activities on the Berkeley campus, maybe more pronounced than in most places. But there were some people on our campus who had consulted for commercial organizations for quite a long time. Howard Schachman, for example, was a consultant for many years to the Spinco Corporation--Spinco made the ultracentrifuge--because he was what they call a power user in today's jargon. He uses the ultracentrifuge in a lot of his work.

There is a long tradition of people in chemistry consulting. There is a long tradition of people in engineering consulting. But I think in the biological sciences it just wasn't done very much. The sixties and seventies were periods where there was a big chasm between business and academia. It developed over the politics of the sixties. There was deep mistrust on both sides of that chasm. Berkeley was always identified as being one of the most leftist places in the country. Whether it truly was or not is another matter.

So I think there was a general distrust of business and business people on campus. But I'm not sure, frankly, that there was such a great love for the business guys at UCSF or Stanford either. They had more reasons to get involved, but even though Bill's gotten very involved obviously in Chiron, he turned down an opportunity to work with Genentech in the early days, for reasons of his own. I don't know exactly why I know he was concerned about a conflict of interest, being chairman of the department at the time.

Hughes: Also, remember the controversy which Genentech caused at UCSF and specifically in the biochemistry department.

¹⁵ On the subject of adopting recombinant DNA, see the oral history retrospective in progress with Berkeley immunologist Marian E. Koshland.

- Penhoet: Sure, the locks on the freezers was an important day in the history of the institution.
- Hughes: That too, but another focus was Herbert Boyer himself, who had a rough time when Genentech was essentially functioning out of his laboratory.¹⁶
- Penhoet: At least in part. I think there was the general suspicion, perhaps overblown, about how anti-business the community was here. The trouble with these kinds of discussions is it's hard for me to put myself back into that environment.
- Hughes: Opinion has swung 180 degrees, hasn't it?
- Penhoet: Yes. So I'm trying to think back, well, am I being objective about this? Hard to judge. It might be better to ask some people who haven't made this transition from academia to industry and back again, to recall the mindset of people of those days.
- Hughes: Well, I talked to Keith Yamamoto at UCSF, who was one of the people really opposed to faculty having commercialial ties.
- Penhoet: Keith was very opposed.
- Hughes: Putting it simplistically, it was easy for a molecular biologist to be anti-commercialization when a molecular biologist, until recombinant DNA arose, had very little to offer to industry.
- Penhoet: Yes, that's right, there weren't many. Pharmaceutical companies employed a few consultants in those days.
- Hughes: Yes. William Rutter being one.
- Penhoet: Bill was employed as a consultant probably since he was twenty-five years old. He did it always after that. But that would have been unusual.
- Hughes: Would it?
- Penhoet: Sure. Not many people [in the life sciences] spent that many years doing consulting.
- Hughes: Anybody else in biochemistry?

¹⁶ The oral histories in progress with Herbert W. Boyer and Keith R. Yamamoto speak to this controversy. Also see the oral history with William J. Rutter.

Penhoet: Well, if you go far enough back. H. A. Barker, for example, used to work for the C&H Sugar Company every summer in the thirties, because he was on a university salary in those days, and there was no NIH and that kind of grant support.¹⁷ So Barker's early research on campus was all supported by the sugar industry. You're right, a lot of these [relationships] are driven by need. In the early days, most professors who needed money for their research got it from some industrial concern or another. Then the NIH came along and they didn't have to do that any more; they got funding with no strings attached and took it. But industry was a significant factor in the early days of the field.

More on Chiron

Initial Recruitment of Scientists

Hughes: Well, in 1993 you wrote an article which listed the minimal number of technologies that went into the commercialization of human insulin--nine different ones.¹⁸ You stated that multiple capabilities were needed to produce a biotech product. How did you recruit people with all those capabilities, and from where? You mentioned having forty people--in the first year of Chiron?

Penhoet: No, by the end of the second year.

Hughes: So what was the mechanism?

Penhoet: Well, first of all, people are generally multi-tasking, so you wouldn't need--

Hughes: A separate person for each task.

Penhoet: That's right; you don't need twelve to twelve.

Well, [recruitment] came in two stages. During the initial stage, we had a significant advantage in the sense that by 1981, when we started Chiron, Bill had been at UCSF for eleven years and I had been at Berkeley for ten years, and Pablo had been

¹⁷ See the oral history in this series with Dr. Barker.

¹⁸ Edward E. Penhoet, "The Future of U.S. Science Policy," *ASM News* 1993, 59:1, 6-7.

working in some combination of Chile and the U.S. for eight years. The net result of this was that there were a lot of alumni of our laboratories around. And because we had been at UCSF and Berkeley for all this time, there were not only alumni of our own labs, but we knew a lot of people who had gotten their degrees in colleagues' laboratories. So we actually wrote down a list of seventeen or eighteen people and said, "These are the people we are going to go and recruit." We may have even included the list in our business plan.

Hughes: Were they all scientists?

Penhoet: Yes.

Hughes: What about attorneys?

Penhoet: Well, we didn't need any. We had nothing to market. We had no intellectual property. We hired an outside attorney, William Green of Brobeck, Phleger, and Harrison,. It was all scientists. In 1983, when we went public, I was the chief financial officer. It was a simple business--forty people. This is not rocket science from a business point of view. You didn't have the products; you basically weren't in business. So we hired only scientists for the first few years.

If you look at the list of seventeen, I think we got fourteen of them to come to work for us, so we were very successful in recruiting these people. And almost all of them had worked in one or another in our laboratories, or in our department. We knew who was good, we knew who we thought we could recruit, and these people knew us. So that was a big advantage for us getting started, in the sense that in those seventeen people, probably most of the skills that were required were resident somehow.

Hughes: Were you hiring for specific technical capabilities, such as DNA sequencing?

Penhoet: Yes.

Hughes: So you were matching individuals to a task more or less?

Penhoet: Yes.

Hughes: You could have been recruiting just good molecular biologists.

Penhoet: Well, but a good molecular biologist in those days was a guy who knew how to clone genes and express proteins. As we grew the company, we often hired people for specific skills. For example,

we knew that there was a scientist named Rick Najarian at Genentech who was really good at sequencing DNA. We needed somebody to sequence DNA; we hired him as basically a DNA sequencer. Today he runs a big part of our computer programs at Chiron, but at that time, we recruited him from Genentech because he could sequence DNA better than anybody else we knew. So some of our people were recruited for specific skills.

The group of seventeen collectively had most of those skills, but it wasn't formal; we didn't, Sally, sit down one day and say, "Okay, how do these seventeen line up with all the skills we need?" They were generally people who were skilled in the art, so to speak, and who were good scientists, and whom we knew we could employ productively.

Recruiting Other Employees

Hughes: At what stage did you have to branch out and begin to get attorneys and scale-up people and whatever other skills Chiron would need? And those needs must have required different channels, which maybe you weren't tapped into initially.

Penhoet: That's for sure. We probably hired our first manufacturing person five years later, '86, '87, something like that.

Hughes: How do you go about finding somebody out of your own field?

Penhoet: Well, if someone asked me what was the most significant management challenge, it's recruiting good people outside your field. I can spot a good scientist a mile away. I can get fooled by a lot of people who tell me how great they are at marketing or some other aspects of this [business]; it's really difficult. Well, the first lawyer we hired was a woman, Jane Stratton, who came to us because she was a personal friend of Bill's daughter, and she turned out to be quite competent and very motivated.

Eventually, we recruited a superior to her, William Green, who incorporated Chiron. But he was working in a law firm in San Francisco at that time, and then when Chiron got to the stage where it needed a full-time in-house attorney, we offered him the job, because we knew he was good because we'd worked with him for seven years by then. He's still there.

Hughes: Did he have a background in biology?

Penhoet: No, only in law. It's not necessary for a corporate attorney. For patent attorneys, yes, they have to know some science.

Chiron's Four Stages of Growth

Penhoet: The company really went through maybe three phases--four now. We went through the first five or six years where we established our credibility, where we established a patent portfolio, where we successfully developed the hepatitis B vaccine, we got the technology working well for other things, we produced several different growth factors--EGF, IGF, et cetera.

Hughes: Hepatitis C came in that period, too?

Penhoet: No, that came later. But the hepatitis C was the end of the first era. We did a lot of things well, but we probably didn't have anything that was going to make us truly successful yet. We were competent, we had developed a number of things, but the first phase ended when we cloned hepatitis C.

When we cloned hepatitis C [1987], and it was clearly established that we were alone with hepatitis C, then the company went through a significant growth phase. That's probably when we hired our corporate attorney to come full time. We had to manufacture the antigens so we scaled up manufacturing. We hired more manufacturing people; we hired regulatory people. We did all this stuff primarily to take advantage of the hepatitis C discovery, and to forward integrate into manufacturing and all the other activities. So that was the second phase.

Simultaneously with that, we started the vision business [Chiron Vision], which was a distraction. It's not biotechnology; we never should have done it. But at the time, we thought it was biotechnology, because there was good evidence that growth factors that we had been working on all along were good for wound healing, particularly in the eye. That's why we started Chiron Vision. So we expanded a lot in the second phase, which was, say, the five years from '87 to '92.

Then the third phase was after we acquired Cetus [1991]. Cetus fell on hard times; put itself up for sale.

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Penhoet: Cetus had essentially traded the rights to PCR [polymerase chain reaction] to Roche for a license to IL-2 [interleukin-2]. Roche

had some IL-2 patents, so Roche gave Cetus a license for IL-2, and Cetus gave Roche the rights to PCR, with a royalty attached. When we negotiated our agreement with Cetus in 1991, Roche already had exclusive rights to PCR with a royalty obligation. The royalty obligation was monetized at that time, and Roche bought out the remaining interest in PCR. But there were no rights left. It was only a revenue stream. The question was whether you got it all then or some later. So that was already done.

The fourth phase came with the Ciba-Geigy (now Novartis) transaction in 1995. In this transaction, Chiron acquired Ciba-Corning diagnostics and doubled in size overnight. At about the same time, the company also acquired two vaccine companies in Europe, Behringwerke and Sclavo. The net result of these transactions was a transformation of the company to a large (7,500 employee) commercial health care company.

Diagnostics

- Hughes: Getting back to hepatitis C: Did that work push Chiron towards the diagnostic area? I realize that you had started Chiron with the idea that diagnostics would be one avenue of research.
- Penhoet: We got in the diagnostic business in a big way because of hepatitis C, because the immediate use of hepatitis C technology was to screen blood, to make sure it was safe for transfusion, and to diagnose patients who had hepatitis C so that you would at least get some guidance about what to do with them. So that drove a big interest in diagnostics. We had had some previous programs in diagnostics. Mickey Urdea's program was fundamentally diagnostic in nature. The DNA--
- Hughes: Probes.
- Penhoet: The probes program had preexisted the discovery of hepatitis C. We were involved in HIV very early on, and the diagnostic tests for HIV were a significant business opportunity. So it wasn't just hepatitis C, but hepatitis C sort of crystallized this whole area for Chiron.

Regional Characteristics of the Biotechnology Industry

Hughes: We've talked about universities and venture capital as some of the ingredients of the biotech industry. What also is there in this region that might account for its flourishing?

Penhoet: [long pause] Well, certainly those two rank so far above whatever's third that I have a hard time coming up with whatever is third. Certainly there were some things stacked against it. There was no tradition of a pharmaceutical industry in California, for example. Syntex was the only pharmaceutical company of any significant size in California.

There are some very general things: Entrepreneurial nature of Californians generally. We talked about this earlier: the special role of Stanford in generating entrepreneurs. What is there about that, I don't know. It's the psychology in the area. Pioneering spirit. Maybe the next wave will be in Alaska, I suppose, where the restless people are.

In addition to venture capital, probably the example set by the electronics industry is important. There's a whole mindset around fear of failure, of risk of failure, which is probably less well developed in California. I know we talked about this before. In Europe, if you go bankrupt, it's a stain on your soul. And to some degree, it probably is in New England as well, where there is a more staid community. I think in California there's a less moral overtone to all these things. You do what you do; if it works, fine; if it doesn't work, that's fine too; people go on and do other things. So it's probably an attitude in the area which is important.

There aren't a lot of other reasons. There certainly were no state subsidies; there were no big programs to attract or retain biotechnology in the Bay Area; there was certainly no local booster clubs trying to make sure that companies did X, Y, and Z. I think it's the concentration of the intellectual climate, concentration of individuals in the field. Nothing [else] comes easily to mind, because money and brains were so dominant as important issues. There's nothing else which is in the same league.

Hughes: Money and universities. And the universities, in contrast to the Silicon Valley experience, remain to this day so absolutely integral to the success of the biotech industry. My understanding of the electronics industry is, maybe the ideas at one stage originated in academia, but the creation of new ideas is now pretty much occurring in industry. That's not true of

biotech. A lot of the ideas, the basic technology, the basic science, is still generated in the university setting.

Penhoet: I think that's right, although I suspect that the electronics industry has been much more dependent on universities than it is willing to admit.

Hughes: Your view gives prime place to the universities. Then of course, to make things go, you have to have investment capital, and you had those two things in spades in this area.

Penhoet: Yes.

Hughes: So maybe you're struggling to find other factors in the growth of the industry because everything else does fade in importance.

Penhoet: Yes, I think that's right. There are some other factors, but they were very modest compared to those two. I'm trying to think of what's unique about the Bay Area. My own perspective is so dominated by science and money that the rest are down the list.

You know, there is a certain quality to this area. Why did the "beat" generation flourish here. Why did the intersection of Haight and Ashbury [streets] define the culture of the sixties? Why are there a lot of gay people here? Why are there a lot of immigrants from all around the world here? There's a certain open culture here which is accepting of new things, different things. Do it your way, it's okay. And that probably is an important thing. If you peel this onion back one level further, the businesses are here because the universities are here. Why are these universities here? There's a reason. They have attracted a certain kind of individual. There are very few places in the world that are as--for the lack of a better word--open-minded as California is. We don't often appreciate enough, I suspect, how accepting we are of alternative lifestyles, people, cultures, all these things. Maybe more than anyplace in the world, San Francisco is a place where people can be themselves.

Pharmaceutical Industry Reaction to Biotechnology

Hughes: You spoke of the pharmaceutical industry not being based on the West Coast. Is that in any way an explanation for why the pharmaceutical industry seemed to be slow in adopting recombinant DNA technology?

Penhoet: Yes, in a sense. The pharmaceutical industry is located where it is because the pharmaceutical industry grew out of the chemical industry. Pharmaceuticals historically developed as byproducts of the chemical industry. A number of chemical companies had what were called fine chemical divisions, complicated chemicals, and they would sell these complex, so-called fine chemicals. Some bright person at some point in time after World War decided that maybe these fine chemicals had some use as medicine.

So after World War II, many chemical companies started drug development programs, and they became successful, but they became successful as ways of expanding the use of their chemical capability. They were all located on the East Coast or the Midwest. They all also had little or no need for extensive knowledge of biology in order to do what they did, because they had big chemical libraries; they tested them on animals; they found one that lowered blood pressure; they found out whether it was safe or not; they give it to people, and that's that. So they weren't mechanism based; they were phenomenologically based.

As a result, first of all, they had a chemist's bias, which was these big ugly molecules that you made with biotechnology were not very attractive as therapeutic agents. And in a sense, they're still right about that. And second of all, they had gotten along quite well without a sophisticated understanding of biology, which was a cornerstone of the biotech industry.

Hughes: Big molecules are hard to administer?

Penhoet: Yes. Proteins are unstable; you can't store them at room temperature; you have to freeze them or lyophilize them or something. I mean, they're just not very friendly to deal with. And those of us in molecular biology at the time had a vision that the laundry list that we were working on, everybody chasing the same products, was going to be expanded. We would discover new genes and new pathways and new hormones and all the rest of the stuff. But the people in the pharmaceutical companies, because of the approach they had taken to it, were not convinced that was the case. So I think they saw a very limited future for this new technology of molecular genetics, because they couldn't see how it was going to fit in their scheme of things, and because proteins were not very user-friendly.

Hughes: Did they think, Well, maybe this new technology has some application in drug production, and if that proves to be the case, then we'll just partner with these new companies?

Penhoet: Sure.

Hughes: That approach was a substitute for actually developing an in-house capability in the new biotechnologies?

Penhoet: Yes. At the time, they couldn't have hired the best people anyway, so in a sense, it was rational for them to take a wait-and-see attitude. They could always use their muscle, because at that time, most pharmaceutical companies didn't have a liberal publishing policy. So most scientists I know wouldn't have gone there if they couldn't publish.

Hughes: Well, and isn't it even more than that, that a scientist in industry was looked down on by academics?

Penhoet: Oh, without a doubt. No question about that.

Hughes: So if you were a top-notch academic, you wouldn't dream of going to work in industry?

Penhoet: A few did, but not many.

The Role of Personality

Hughes: What are characteristics of a successful bioentrepreneur? Is it possible to generalize?

Penhoet: Well, it has to be at some level.

Hughes: You could tell me, "That's an impossible question, Sally; there is no general personality profile."

Penhoet: No, I don't think it's impossible. People who have been successful at this, if you look at them as a class, what characteristics do they share? Well, they're almost all energetic as a class. I think most people who have done this and done it well have a high energy level.

They all have to have good sales skills, not sales in the narrow sense of that word. But in order to be an effective leader, you have to convince somebody else to do what you want him to do. So you have to sell your ideas; you have to sell your concepts. Take our own experience. If somebody said, "Hey, Penhoet, what did you do well for Chiron?" I sold. We had to sell people on coming there; we had to sell investors dozens of times on investing money in the company; we had to sell partners on the program we did. So although most scientists will probably recoil from the description of themselves as sales people, to be

a successful entrepreneur, you've got to be very good at convincing other people to follow you, wherever you're going, and to sell them on your notion. So I think good sales skills are also very important, and they're very widespread among the people who have done this and been successful at it.

It goes without saying that you've got to be smart, because you won't be there unless you are. I think you have to have an optimistic outlook. Most successful entrepreneurs, maybe all, are fundamentally optimists by nature.

Hughes: Does that correlate with risk tolerance?

Penhoet: Yes, sure, because your perceived risk is lower. If you're an optimist, you don't think you're going to fail. An optimist and a pessimist will look at the same situation, and one of them sees it as tremendously risky. Which one is it? It's the guy who is fundamentally pessimistic about the future and says, "This is a terribly risky thing you're about to do." The optimist looks at the same situation and says, "Well, it's not so risky; I'll make it work." The perception of risk and the outlook of an individual are highly linked characteristics. I think without question, it takes an optimistic personality. Otherwise, people wouldn't do it.

People who are successful in leadership roles somehow stimulate in the people around them a desire to follow. There's a charisma, or whatever it is, that inspires people. To be successful in our business, every aspect is related to real effort on people's parts to make it work. It's not just the leaders; everybody down to the technicians has to be committed to success. The leadership of these organizations has to be able to inspire confidence and commitment. It's particularly true in startup companies as you go forward. People aren't going to stay if their perception is that the company's not being well led.

Hughes: As the successful biotech companies such as Chiron grow larger, is there a danger of losing that personal motivating power?

Penhoet: Well, yes, I'm sure. It has to become institutionalized to some degree. In large companies, you probably will lose it; it's inevitable. It's already been lost to a great degree at Chiron. It's a different place today than it was five years ago, ten years ago, because institutional things take over. I joke with people that the irony of being successful in biotechnology is you build the company that you never would have gone to work for yourself. And to some degree it's true. If you're successful, you'll create a large company. If somebody had come to me in 1981 and said, "Hey, Penhoet, do you want to go to work for this

company that has 7,000 employees?," I wouldn't have even been tempted for a microsecond. So it is ironic, but that's the nature of the business.

Major Contributions

Hughes: One last question: what do you look back on as Chiron's greatest contribution?

Penhoet: Without question, the discovery of hepatitis C. Hepatitis B would have gotten done whether we did it or not. There were too many groups working on it; the competition was fierce. That's not to take anything away from the pioneering work that Bill and Pablo did. But hepatitis C was an unusual contribution, and I don't think anybody understood how important it was, even we to some degree, until after it had been done. Ten years later, we're gaining appreciation for how important that is. So from the standpoint of contribution to mankind, that certainly was the most important single thing that Chiron has done.

Hughes: What is your greatest personal contribution?

Penhoet: As an individual, my most important contribution is probably facilitating it all because I am good at translating science into business and vice versa. I have not a unique but an unusual ability to communicate both with business people and with scientists. So I could effectively raise money; I could enlist the support and cooperation of people inside the company who weren't scientists to buy into the science mission of the organization. So combining the elements is probably my biggest personal contribution to the enterprise.

Hughes: Do you want to say anything else?

Penhoet: Well, not now.

Hughes: Thank you.

TAPE GUIDE--Regional Characteristics of Biotechnology

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**Schering-Plough**

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Telephone (908) 298-4000

HUGH A. D'ANDRADE

**Vice Chairman and Chief Administrative Officer
Schering-Plough Corporation
Kenilworth, New Jersey**

Hugh A. D'Andrade is vice chairman and chief administrative officer and a member of the board of directors of Schering-Plough Corporation, a research-based company engaged in the discovery, development, manufacturing and marketing of pharmaceutical and health care products worldwide.

He has overall responsibility for Schering-Plough's investor relations and corporate communications, human resources, environmental audits and management systems, as well as venture capital activities. He also directs the Company's strategic planning efforts and is involved in the management of biotechnology research activities, serving as policy board chairman of the Company's DNAX Research Institute.

Mr. D'Andrade was elected to the board of directors of Schering-Plough in 1984. From 1978 through 1980, he served on the board of directors of ALZA Corporation, a world leader in drug delivery technology. In 1981, Mr. D'Andrade was elected to the board of directors of Biogen N.V., a biotechnology firm engaged in the development of human therapeutics. He served on that board and as chairman of its compensation committee until 1986. Mr. D'Andrade served on the board of directors of Molecular Devices Corporation, a diagnostics firm based in Palo Alto, Calif., from 1984 through 1989.

Mr. D'Andrade is a director of the Biotechnology Industry Organization and its predecessor organization and served as chairman from October 1988 through 1989. He is a member of the boards of directors of AutoImmune Inc., Chitogenics, Inc. and

Atlantic Mutual Companies. He also serves on the board of trustees of Drew University and is chairman of its academic policy committee. In addition, he serves on the board of Overlook Hospital Foundation and is a member of the Columbia Law School Board of Visitors, the American Bar Association and the New Jersey Bar Association.

Mr. D'Andrade was elected to his present position at Schering-Plough effective January 1, 1996, after serving as executive vice president - administration since 1984. Prior to joining the Company in 1981 as senior vice president - administration, Mr. D'Andrade was senior vice president - administration and counsel of the Pharmaceutical Division of Ciba-Geigy Corporation in Summit, N.J. He joined Ciba Corporation, now a division of Ciba-Geigy, in 1968 as general attorney and subsequently held several positions in the law department before becoming vice president - administration and counsel in 1977.

Born in Metuchen, N.J., in 1938, Mr. D'Andrade holds a bachelor's degree in economics from Rutgers University. He earned a law degree, cum laude, from Columbia University School of Law in 1964. He served as law secretary to the Honorable Frederick W. Hall, associate justice of the New Jersey Supreme Court, in 1964 and 1965, after which he was an associate in the Newark, N.J., law firm of Toner, Crowley, Woelper & Vanderbilt for three years.

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David P. Holveck
Chief Executive Officer

Mr. Holveck was named Chief Executive Officer in 1992 and was elected to the company's Board of Directors in 1994. Prior to his current position, he was, successively, Vice President of Marketing and Sales, Executive Vice President of North America, Executive Vice President of Diagnostics, President of Diagnostics, and President and Chief Operating Officer of the company.

Mr. Holveck joined Centocor in 1983 from the General Electric Company, where he developed and implemented worldwide marketing strategies for GE's computerized tomography and digital X-ray medical imaging systems. Previously, he held positions of increasing responsibility in the medical products businesses of Corning Glass Works and Abbott Laboratories.

He is on the Board of Directors of CV Therapeutics, Inc. and the Pharmaceutical Research & Manufacturers of America (PhARMA) and also is a member of the Advisory Board of Micromet GmbH in Munich, Germany. In addition, he serves as Chair of the Biotech Network Segment of Pennsylvania Governor Tom Ridge's "Technology 21" initiative. In 1997, Mr. Holveck was honored as Man of the Year by the Crohn's & Colitis Foundation of America, Greater New York Chapter.

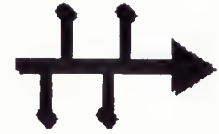
Mr. Holveck received his Bachelor of Science degree in Education/Science from West Chester University.



History/ Timeline

- [Centocor Profile/History & Fact Sheet](#)
- [What is Biotechnology](#)
- [Divisions & Products](#)
- [Annual Report](#)
- [Letter to Investors](#)
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Centocor History



The discovery of monoclonal antibodies (mAb) in 1975 began a revolution in human health care. These exquisitely specific natural proteins quickly found their first application in diagnostic tests to detect and monitor disease. Accurate detection can have a profound effect on both the quality of life and the chances for survival of patients suffering from deadly diseases such as cancer. Through extensive research and development, monoclonal antibodies can now be used to help find new and innovative therapeutic solutions.

Centocor has been in the forefront of the commercial development of monoclonal antibodies since they emerged from academic research laboratories in the late 1970s. Centocor began operations in the fall of 1979 and concentrated on obtaining financing, recruiting personnel, and equipping a laboratory facility. During the next year, Centocor increased research and development activities, including the initiation of research agreements at outside institutions. The initial focus of the company was to develop diagnostic assays using the monoclonal antibody technology.

With a combination of intensive research, development, manufacturing and financing, Centocor was on its way to becoming a leading company in the new and emerging field of healthcare known as biotechnology. As the new century dawns, Centocor is one of the world leaders in the healthcare technology industry, poised to meet the public health challenges facing our changing world.

Centocor Timeline of Major Events

Mid-1970s

Researchers at the Laboratory for Molecular Biology in Cambridge, U.K., successfully fuse a myeloma cancer cell with an immune cell to create a new hybrid, a hybridoma. The science platform of monoclonal antibodies is born.

1979

Business plan for "Hybridomas Incorporated" formulated.

May 16, 1979

Centocor is incorporated.

October 1979

Development agreement signed for one year with Abbott Laboratories for Centocor, Inc. to "develop and transfer anti-cholylglycine monoclonal antibodies" for use by Abbott.

1980

Total revenues for the year are \$153,333.

1981

Successful development of an assay to detect a gastrointestinal cancer-related substance in patient serum. This assay would become CA 19-9™.

1981

Total revenues exceed \$1 million for the first time.

1982

The U.S. Food and Drug Administration (FDA) approves first Centocor product, a diagnostic test for the detection of the rabies virus.

June 1982

Centocor consolidates operations in Malvern, Chester County, Pennsylvania. The Diagnostics research and manufacturing facility in Malvern is licensed by the FDA.

September 1982

Centocor's first cancer diagnostic product, CA 19-9, is introduced in more than ten countries outside the U.S. CA 19-9 is a serum tumor marker test for gastrointestinal cancers.

December 1982

Centocor raises \$21 million in its initial public stock offering. Shares begin trading on the NASDAQ market, under the symbol CNTO, at \$14.40.

January 1983

FDA approves the first hepatitis B test, which was developed by Centocor, using hybridoma technology.

February 1983

Centocor and Warner-Lambert announce marketing agreement for hepatitis B diagnostic product.

1984

Total revenues exceed \$10 million for the first time.

1985

Centocor Europe B.V. is established in Leiden, The Netherlands.

September 1986

The 40,000-square-foot C.B.V. Leiden production facility becomes fully operational.

June 1987

CA 125™, a diagnostic serum tumor marker test for ovarian cancer, is approved by the FDA.

October 1987

Nippon Centocor K.K. opens in Tokyo.

1987

Total revenues exceed \$50 million for the first time.

January 1992

Centocor U.K. Ltd. manufacturing facility established in Guildford, Surrey, in the United Kingdom.

1992

Total revenues exceed \$100 million for the first time.

March 1993

EPIC trial results released. Patients undergoing high-risk balloon angioplasty respond to an "experimental drug" known as 7E3 (ReoPro®). Results show a 35% reduction at 30 days of the occurrence of death, heart attack and the need for emergency repeat angioplasty.

June 1993

Eli Lilly and Company signs exclusive worldwide marketing agreement for 7E3 (ReoPro).

October 1993

Results of 17-1A (Panorex®) trial are announced. Investigators say the drug has a potential use as an adjuvant treatment in patients with colorectal cancer. Of 189 patients enrolled, the overall death rate after a median follow-up of five years was reduced by 30 percent.

November 1993

Centocor and Wellcome plc (now Glaxo Wellcome) announce a marketing agreement for Panorex.

December 1993

Centocor files a Product License Application for 7E3 (ReoPro) with the FDA as well as the European Union's Committee for Proprietary Medicinal Products (CPMP).

November 1994

ReoPro receives first approval in Sweden

December 1994

ReoPro is cleared for marketing in United States by the FDA and by the European Union's regulatory body, CPMP.

January 1995

Panorex is cleared for marketing by Germany's Paul Ehrlich Institute.

February 1995

ReoPro is launched in the U.S. and Panorex is launched in Germany.

December 1995

Two ReoPro trials, EPILOG (all-comer angioplasty patients) and CAPTURE (refractory unstable angina patients eligible for PTCA), are halted due to positive interim results.

December 1995

End-user sales of ReoPro top \$22 million in the first year of launch.

January 1996

Centocor files registration statement for follow-on equity offering of 3.5 million shares. Proceeds will be used for debt reduction following the offering.

May 1996

Centocor announces positive results for a Phase II trial using Avakine in the acute setting of Crohn's disease.

July 1996

Centocor is named "Best Biotechnology Company for 1995" by *Medical Advertising News*, a monthly trade publication for the pharmaceutical business and marketing community.

August 1996

Centocor signs an agreement with Fujisawa Pharmaceutical Co., Ltd. under which Fujisawa will be the exclusive distributor of ReoPro in Japan once the drug receives approval there. Phase II trials are expected to begin in Japan later this year.

November 1996

Centocor reports positive results from the EPILOG trial, showing that ReoPro continues to have a favorable impact for angioplasty patients six months after the operation, with the number of deaths and heart attacks reduced by 46 percent.

January 1997

Centocor reports earnings of \$2.9 million, or \$0.04 per share, for the three months ended December 31, 1996, its first profitable quarter in the 1990s.

End-user sales of ReoPro grow to \$149.3 million for 1996.

February 1997

Centocor files claims with the FDA for expanded use of ReoPro to include all patients undergoing angioplasty and unstable angina patients unresponsive to conventional therapy and scheduled for angioplasty.

April 1997

Centocor reports positive results from a pivotal trial for

Avakine in Crohn's patients who have fistula, a severe complication of the disease. Based on these data, Centocor announces that it will file for FDA approval of Avakine in Crohn's disease later in 1997.

June 1997

Centocor reaches agreement to sell its diagnostic manufacturing facility, located in Guildford, England, and its related infectious disease product line to Trinity Biotech plc, of Dublin, Ireland. The sale results in a one-time charge to Centocor's earnings of \$4.6 million, or \$0.06 per share.



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June 1997

Centocor reaches agreement to sell its diagnostic manufacturing facility, located in Guildford, England, and its related infectious disease product line to Trinity Biotech plc, of Dublin, Ireland. The sale results in a one-time charge to Centocor's earnings of \$4.6 million, or \$0.06 per share.

November 1997

Centocor presents clinical data at the American College of Gastroenterology that shows infliximab may be useful for treatment of fistula(s), a serious and painful complication of Crohn's disease.

November 1997

The FDA approves an expanded label for ReoPro® as adjunctive therapy in patients undergoing percutaneous coronary intervention (PCI), such as balloon angioplasty, atherectomy and stent placement, as well as in unstable angina patients not responding to conventional medical therapy when PCI is planned within 24 hours.

November 1997

Results from a Phase III clinical trial presented at the American College of Rheumatology show infliximab may be an effective treatment for rheumatoid arthritis.

November 1997

The European Union formally adopts the expanded label for ReoPro® that was recently approved by the FDA.

December 1997

As part of a management succession plan, Joseph C. Scodari is elected president and chief operating officer for Centocor and Dominic J. Caruso is elected as senior vice president and chief financial officer. Scodari succeeds as president David P. Holveck, who continues as chief executive officer.

December 1997

Centocor files a Biologics License Application (BLA) with the FDA for infliximab for the treatment of moderately to severely active Crohn's disease, including fistulizing Crohn's disease.

January 1998

Total revenues for 1997 reached a record \$200.8 million.

February 1998

Centocor acquires U.S. and Canadian rights for Retavase® (reteplase)--- a recombinant biologic administered for treatment of acute heart attacks to improve blood flow to the heart --- for \$335 million in cash.

February 1998

The FDA grants the BLA for infliximab a priority review, which means it will take action on the application within six months.

February 1998

Centocor issues \$460 million convertible subordinated debt to pay for the acquisition of Retavase® and plant expansions.

March 1998

Centocor officially launches its commercial cardiovascular salesforce, promoting Retavase® for acute myocardial infarction. Data presented from the EPILOG Stent trial during the American College of Cardiology demonstrates that ReoPro® -treated patients showed a statistically significant improvement versus patients receiving stents without ReoPro in the composite primary endpoint of death, heart attack or urgent intervention at 30 days.

April 1998

Centocor and Schering-Plough Corporation sign an agreement giving Schering-Plough international distribution rights, excluding the U.S., Japan and parts of the Far East, to Centocor's infliximab for Crohn's disease and rheumatoid arthritis.

May 1998

An advisory committee to the FDA votes unanimously to recommend approval of infliximab for treatment of patients with moderate to severe Crohn's disease in whom conventional therapy is inadequate and for those patients with fistula(s).

May 1998

An article in the *Journal of Clinical Oncology* shows that, after seven years, treatment with Panorex® (edrecolomab), a monoclonal antibody, reduced death and recurrence of disease in patients with Dukes' C colorectal cancer.

May 1998

Centocor begins co-promotion of ReoPro® in the U.S. with Eli Lilly and Company.

June 1998

Quarterly sales of ReoPro® to customers by Eli Lilly reach \$100 million for the first time.

July 1998

The 30-day results of the EPISTENT trial (formerly EPILOG Stent trial) are published in *The Lancet*, a leading medical journal.

July 1998

Centocor announces that the new brand name for infliximab, formerly referred to as Avakine™ and as cA2, is Remicade™.

August 1998

The FDA grants marketing clearance to Remicade™ (infliximab), a novel monoclonal antibody for treatment of Crohn's disease and the first new product in 30 years indicated for this serious gastrointestinal condition.

August 1998

The 6-month results from the EPISTENT trial are presented at the European Society of Cardiology. The combined use of ReoPro® with stents in patients undergoing coronary interventions reduces the risk of death or heart attack by more than 50 percent.

September 1998

Centocor begins shipping Remicade™ to distributors nationwide.

October 1998

The six-month results from the EPISTENT trial are presented in the U.S. for the first time at the Transcatheter Cardiovascular Therapeutics (TCT) conference in Washington, D.C. Results were previously presented at the European Society of Cardiology in August.

October 1998

Remicade™ is now available nationwide for the treatment of Crohn's disease.

October 1998

During Centocor's first security analyst briefing in New York, the company announced that it is expanding its clinical development program to aggressively pursue additional indications in new treatment areas for existing products. The two primary targets are cardiovascular and autoimmune/anti-inflammatory.

November 1998

Centocor announced the launch of TIMI 19 (Thrombolysis in Myocardial Infarction, Early Retavase®), a trial that will investigate the efficacy and safety of expediting the administration

of the fibrinolytic agent Retavase® (reteplase) in the ambulance before patients reach the hospital.

November 1998

In the one-year follow-up of the largest coronary stent trial ever conducted (EPISTENT), patients with ischemic heart disease who received the combination of the antiplatelet monoclonal antibody drug ReoPro® with stent placement significantly reduced their risk of death by 57 percent compared to patients undergoing stenting alone. Data were presented at the American Heart Association meeting in Dallas.

November 1998

Remicade™, the first monoclonal antibody under investigation for rheumatoid arthritis, reduced signs and symptoms of the painful and chronic joint condition in 52 percent of patients receiving the drug compared to 20 percent of those on placebo. Results from this Phase III trial were highly significant over the 30-week timeframe compared to placebo. Data were presented at the American College of Rheumatology meeting in San Diego.

November 1998

Centocor announced the closure of the previously reported sale of its oncology diagnostics business to Fujirebio, Inc. of Japan, for approximately \$37.5 million in cash.

December 1998

Centocor reaches an agreement with DuPont Pharmaceuticals to end the co-promotion of Retavase®, giving Centocor exclusive rights to market the product in the U.S. beginning January 1, 1999.

December 21

Centocor's Board of Directors elects Joseph C. Scodari, president and chief operating officer of Centocor, to the board beginning January 1, 1999. His appointment increases the number of board members to 10.

January 26, 1999

Centocor submits a supplemental application to the FDA for Remicade to treat rheumatoid arthritis.

*Curriculum Vitae***EDWARD E. PENHOET**

BIRTHDATE: December 11, 1940

BIRTHPLACE: Oakland, California

CITIZENSHIP: USA

MARITAL STATUS: Married, two children

EDUCATION:

1958-1963	Stanford University, A.B. (Biology) 1963
1964-1965	University of Illinois
1965-1968	University of Washington, Ph.D. (Biochemistry) 1968
1969-1971	University of California, San Diego-postdoctoral

EMPLOYMENT HISTORY:

1998 - present	Dean, School of Public Health University of California, Berkeley Professor, Health Policy and Administration Professor, Molecular and Cell Biology University of California, Berkeley
1981-1998	President and Chief Executive Officer Chiron Corporation Emeryville, California
1992-1998	Adjunct Professor of Molecular and Cell Biology, University of California, Berkeley
1983-1992	Adjunct Associate Professor of Biochemistry, University of California, Berkeley
1977-1983	Associate Professor of Biochemistry, University of California, Berkeley
1971-1977	Assistant Professor of Biochemistry, University of California, Berkeley
1970-1971	Acting Assistant Professor of Biochemistry, University of California, San Diego
1968-1971	NIH Postdoctoral Fellow, University of

Edward E. Penhoet, Ph.D.
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California, San Diego

1965-1968 NIH Trainee, University of Washington

1964-1965 NIH Trainee, University of Illinois

1962-1963 Undergraduate Research Assistant and Teaching Assistant,
Stanford University

HONORS/AWARDS: 1974 Dreyfus Foundation Teacher-Scholar Award

1991 Distinguished Service Award, University
of California, Berkeley

Northern California Entrepreneur of the Year Award presented
by Ernst & Young and Inc. Magazine (1992)

Northern California Entrepreneur of the Year Award presented
by the Harvard Business School

Distinguished Alumni Award; Oakland Public Schools (1993)

University of California, San Diego Regents' Lecturer (1994)

COMMUNITY SERVICE

SERVICE TO THE LOCAL COMMUNITY:

Chairman, Chabot Observatory and Science Center

Trustee, Oakland Museum

Member, Oakland CEO Council

Member, Bay Area Bioscience Center Board

Member, Bay Area Council

Member, Bay Area Economic Forum

SERVICE TO THE STATE OF CALIFORNIA:

Chairman, California Healthcare Institute

Member, California Governor's Biotechnology Council

Director, California Public Health Foundation

Member, California Business Higher Education Forum

SERVICE TO NATIONAL ORGANIZATIONS:

Member, National Research Council Commission on Life Sciences

Member, National Research Council Committee on National Needs for Biomedical & Behavioral Scientists

Member, National Research Council Committee of Undergraduate Science Education

Advisor, Committee on Science, Space & Technology - US House of Representatives (1992)

Member, NIH Economic Roundtable on Biomedical Research

Member, Board of National Foundation for Biomedical Research of the NIH

Chairman, NIH Forum on Sponsored Research Agreements, Bethesda, Maryland (1994)

Member, National Science Foundation National Visiting Committee

SERVICE TO EDUCATIONAL INSTITUTIONS:

Member, Dean's Policy Advisory Council, UCB School of Public Health

Member, University of California (systemwide) Biotechnology Advisory Committee

Member, UC Davis Medical School Board of Visitors

Member, Lester Center Board of Advisors of the Haas School of Business

Member, UCSD Natural Sciences Council

Member, UCB Foundation Board of Trustees

SPECIAL PRESENTATIONS:

UC Board of Regents

- University of California Role in Biotechnology
- Development of STAR program- a combined UC Research Initiative

Stanford Meeting on Career Opportunities

UCSF Meeting on Career Opportunities

Haas School of Business (numerous presentations)

Cornell University Biotechnology Program

American Academy of Arts & Sciences

PROFESSIONAL SOCIETY MEMBERSHIPS:

American Society for Biochemistry and Molecular Biology

American Association for the Advancement of Science

American Chemical Society

PUBLICATIONS

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UCB COURSES

Spring '97	MCB 102	Survey of the Principles of Biochemistry & Molecular Biology
Spring '96	MCB 290	Graduate Seminar on "Biotechnology: Product from Biology"
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Spring '93	MCB 102	Survey of the Principles of Biochemistry & Molecular Biology
Spring '92	MCB 215	Molecular Biology of Animal Viruses

Chiron President Quits Post

Emeryville biotech firm
had disappointing year

By Peter Sinton
Chronicle Senior Writer

Chiron, the second-largest biotech company, announced yesterday that co-founder Edward Penhoet plans to step down as president and chief executive.

Last year was not a banner year for the Emeryville-based company. There were both product and profit disappointments and Chiron shares lost about a third of their value. But Penhoet said that it was his decision to relinquish the CEO post.

"I came to the conclusion that I've been doing two full-time jobs," said Penhoet, 56. In addition to the normal executive duties of running the business, he increasingly has become an industry spokesman, serving on a dozen scientific boards and committees.

Chiron hopes to hire a new CEO within three to six months and it is looking both inside and beyond the health sciences field for an executive with plenty of experience running efficient organizations and maximizing the commercial potential of research and development.

Penhoet will become vice chairman, responsible for developing policies, dealing with government and industry groups and overseeing research collaborations.

Chiron also announced that co-founder William Rutter, 69, will remain chairman but will give up some day-to-day responsibilities to focus on strategic planning.

"The company has grown nicely with these two guys at the helm," said Hambrecht & Quist analyst Richard Van den Broek. "They've done a great job creating a well-diversified, one-stop shop for investors interested in all the key areas of the industry, including diagnostics, vaccines and gene therapy. The next step is growing earnings and that's a more difficult

nut to crack."

Over the past 16 years, Chiron has grown from a research outfit with 15 employees into a \$1.3 billion company with four commercial businesses and significant research operations that together employ 7,400 people in 30 countries.

Chiron's stock soared in 1995 as clinical trials of seven potential drugs all turned out positive. In addition the company made four acquisitions that added more than 4,000 employees and more than doubled revenues to \$1.1 billion.

Last year's results were just the contrary. There were some problems integrating the company's expanded operations, while sales of some Chiron products, such as the multiple sclerosis drug Betaseron, were confronted by competing drugs.

In one of the worst blows, Chiron's stock lost 18 percent of its value November 25 after the company scrapped develop-



**Co-founder,
chief executive
and president,
Edward Penhoet**

ment of a potential vaccine against genital herpes. "That was a big setback," said Van den Broek. Yesterday Chiron's stock dipped 38¢ to \$18.63.

Chiron is 47-percent owned by Novartis Ag, the Swiss pharmaceutical giant that resulted from the combination of Ciba Geigy and Sandoz last month. Although Novartis looks to Chiron as a tool for discovering technology and developing new therapeutic products, some analysts suggest that Chiron also may be feeling pressure to be more profitable.

from University of California, Berkeley
School of Public Health Highlights,
n.d. [mid-1998]

A Bold New Leader for a Brand New Century

Co-Founder, former president and chief executive of Chiron is named new dean

The term entrepreneur - meaning one who organizes, manages, and assumes the risks of a business or enterprise - is not a word one typically associates with the field of public health; however, it has often been used to describe the new dean of UC Berkeley's School of Public Health, Edward E. Penhoet, PhD, whose tenure began on July 1, 1998.

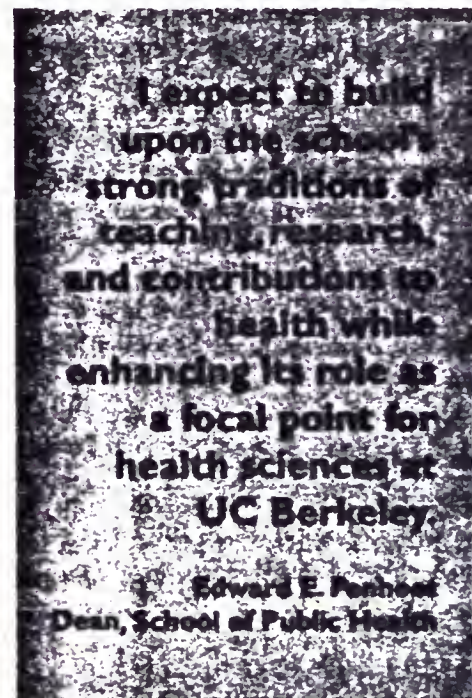
A respected biochemist, Dean Penhoet is widely regarded for his pioneering role in the development of the biotechnology industry. In 1981, he and Dr. William Rutter cofounded Chiron, a global leader in applying biotechnology and other techniques of modern biology to develop products that have a goal of lowering the overall cost of healthcare and improving the quality of life by diagnosing, preventing and treating disease.



Dean Penhoet served as Chiron's president and chief executive officer for 17 years, overseeing the company's expansion from a small Emeryville-based research enterprise with 15 employees to the world's second largest biotechnology company, employing more than 7,500 people in facilities on four continents with annual revenues exceeding \$1.2 billion.

"His expertise and leadership will maximize the strengths of the School of Public Health on the campus," said Chancellor Robert M. Berdahl in announcing Dr. Penhoet's selection as the eighth dean of the School of Public Health.

A native of Oakland, California, Dean Penhoet is a graduate of Stanford University and earned his PhD in biochemistry from the University of Washington in 1968. In 1971, he began his association with the Berkeley campus, serving as a faculty member in the Department of Biochemistry for 10 years.



"I'm very pleased to have the opportunity to return to UC Berkeley as dean at the School of Public Health," said Penhoet. "The appointment represents a fresh challenge and one that I believe will benefit from the integration of academic and commercial viewpoints."

"Ed is no stranger to the school," said his predecessor, former dean Patricia Buffler. "As a member of our Policy Advisory Council since 1993, he has been instrumental in helping the school position itself for the new century by expanding its constituencies, strengthening its programs and educating tomorrow's public health leaders. I am delighted that someone of Ed's caliber and vision is leading us into the next millennium."

"I expect to build upon the institution's strong traditions of teaching, research, and contributions to health, while enhancing its role as a focal point for health sciences at UC Berkeley," said Dean Penhoet. "Additionally, I hope to foster interactions with other UC campuses - particularly UCSF - and to maximize the positive impact of the school on public health in the U.S. and throughout the world."

"Ed Penhoet has shown extraordinary leadership in his work at Chiron," said UC Berkeley's Executive Vice Chancellor and Provost Carol T. Christ. "His management skills, his ability to build consensus, his connections to biological research inside and outside the university, and his loyalty and love for the campus make him a wonderful choice to lead the School of Public Health. I am very excited to be working with him."

Ed Penhoet has shown extraordinary leadership ... His management skills, his ability to build consensus, his connections to biological research inside and outside the university, and his loyalty and love for the campus make him a wonderful choice to lead the School of Public Health.

**Carol T. Christ
Executive Vice Chancellor
& Provost, UC Berkeley**

While leaving his position as a tenured faculty member in 1983 to focus on building Chiron, Dean Penhoet has maintained close contact with the university, teaching an undergraduate biochemistry course almost every year and receiving the first Distinguished Faculty Award for the Department of Molecular and Cell Biology in 1991.

He is also active on the UC Systemwide Biotechnology Advisory Committee, the UC Berkeley Chancellor's Biotechnology Planning Board and the advisory board for the Lester Center for Entrepreneurship and Innovation at UC Berkeley's Haas School of Business.

Nationally, Dean Penhoet has served on three National Research Council boards, including the Commission on Life Sciences, the Committee

for Undergraduate Science Education and the National Needs for Biomedical and Behavioral Scientists assessment. He is also chairman of the California Healthcare Institute and is on the boards of directors of many other institutions.

Dean Penhoet's honors are many and include the Camille and Henry Dreyfus Teacher-Scholar Award, the Ernst and Young Northern California Entrepreneur of the Year Award and the Harvard Business School's Northern California Alumni Chapter Entrepreneur of the Year Award.

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